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Bad winter ahead for the pneumococci

STORMY DAYS are usually followed by sharp increases in the incidence of upper respiratory infections, often the prelude to pneumococcal pneumonia. Fortunately, physicians are prepared to combat the pneumococci with sulfonamides and penicillin.

Although sulfonamides are generally effective, problems sometimes arise in their administration. In the patient with cardiac or renal disease, it may be difficult to maintain proper fluid balance. This imbalance may lead to urinary tract complications. Others may experience untoward toxic effects or lack of response to the drug. In these cases, Penicillin, Lilly, is particularly valuable. While the intramuscular injection of 10 to 15 thousand units every three hours throughout the night and day might be helpful, doses of 20 thousand or more units at the same intervals are preferable. Penicillin, Lilly, is available in 20-cc. ampoules containing 100,000, 200,000, or 500,000 units.

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The Journal of Pediatrics

VOL. 29 NOVEMBER, 1946 NO. 5

Original Communications

INFANTILE CORTICAL HYPEROSTOSES

JOHN CAFFEY, M.D.
NEW YORK, N. Y.

DURING the spring of 1938 we studied an infant whose principal lesions were scattered swellings deep in the soft tissues and scattered cortical thickenings in several bones. After an extensive investigation no cause for the changes was found, and it was evident that this patient suffered from none of the recognized conditions in which cortical thickenings had been found previously, such as scurvy, rickets, syphilis, bacterial osteitis, neoplastic disease, or traumatic injury. In a specimen of the clavicle, simple hyperplasia of the cortex was demonstrated microscopically and there were no signs of an inflammatory cellular reaction or of subperiosteal hemorrhage. This patient was described in a discussion of the nonspecificity of cortical thickenings as related to the diagnosis of infantile skeletal syphilis in 1939.[1]

Three similar cases were encountered during 1939, 1940, and 1944. The group of four cases was reported as a new infantile syndrome under the title "Infantile Cortical Hyperostoses" in 1945.[2] In this paper we pointed out that a group of infants with similar manifestations had been recognized independently during the same period by Dr. Francis Scott Smyth at the University of California Hospital in San Francisco. The California cases have now been reported under the title "Periosteal Reaction, Fever and Irritability in Young Infants: A New Syndrome?"[3]

The three findings common to all of our patients were: (1) tender swellings deep in the soft tissues; (2) cortical thickenings in the skeleton; and (3) onset during the first three months of life. In all specimens of the skeletal lesions the findings were similar, cortical hyperplasia under a proliferating periosteum. Several bones were affected in each patient, but the distribution varied in different patients. Hyperostosis was demonstrated roentgenographically in the mandible, clavicles, scapulas, ribs, and the tubular bones of the extremities. All of the soft tissue swellings were deep and firm; none showed pitting on pressure, none were overly warm or discolored. Regional lymph nodes were not enlarged. The distribution of the soft tissue swellings was roughly the

From the Pediatric Department, College of Physicians and Surgeons, Columbia University, and the Babies Hospital.

same as that of the cortical hyperostoses, but small hyperostoses were visualized roentgenographically in several sites where soft tissue swellings had not been recognized clinically.

Other manifestations which were present in some patients but lacking in others were fever, pleurisy, anemia, and increase in the sedimentation rate of the erythrocytes. The course of the active disease was characteristically uneven. The fever was irregular. Soft tissue swellings appeared in one site when earlier swellings in another site were disappearing; also, the swellings recurred in the same site after partial or complete disappearance. All patients recovered after variable periods of many weeks or months. The cortical hyperostoses were visible roentgenographically months after the fever had subsided and after the soft tissue swellings had disappeared.

After prolonged investigation of four patients, the cause remained undetermined. Bacteriologic and serologic study of the patients and bacterial cultures of specimens removed from affected bones yielded no evidence of bacterial infection. Rickets and scurvy could be excluded on all counts. Traumatic injury was not observed in a single case either at home or in the hospital. Viral infection and allergy were considered as other possible causes but were not sufficiently investigated to either prove or disprove their causal significance.

This report contains data on six additional infants who show the characteristic findings of infantile cortical hyperostoses. Two of them were studied at the Babies Hospital. Four were recognized and investigated in other clinics by colleagues to whom I am deeply grateful for their interest and cooperation.

CASE REPORTS

CASE 1.—L. M., a white female, was first seen at the age of 6 months with the chief complaint of swelling of both cheeks for a period of five weeks. The mother was 39 years of age; she had eaten a normal diet and had been healthy during the pregnancy.

The patient was delivered after a normal gestation and was normal during the neonatal period. She thrived and developed normally on an evaporated milk formula; cereal, fruit, eggs, vegetables, and beef juice had been added to the diet at appropriate intervals. Vitamin D and orange juice were taken daily after the first week of life; for several weeks she had taken 3 ounces of orange juice daily. At 6 months she weighed 7.1 kg.

Present Illness.—At 4 months she began to be irritable at night; she awakened frequently and whined. At 4½ months her pharynx was said to have been inflamed and she had a fever; sulfonamide drugs were given for one week. Then swellings suddenly appeared on both sides of her face and the fever continued at a level of about 101° F. At the onset the swellings were tender and the patient drooled much saliva, especially at night. The sulfonamide therapy did not affect the swellings or the fever and after a few days she was admitted to a hospital for penicillin treatment. The latter had no beneficial effect on the swellings and the temperature remained above 101° F.

In the first examination at the Babies Hospital when she was 6 months of age, conspicuous facial swellings were still evident (Fig. 1*A*). They were firm and diffuse but not tender. The major portions of the swellings were located in the cheeks and submaxillary regions; the parotid regions were relatively free. The swellings were not fluctuant, were neither hot nor reddened, and regional lymph nodes were not enlarged. The buccal swellings protruded into the mouth and the oral mucous membrane overlying the internal swellings was normal. The openings of the parotid ducts were not visible. Motion of the mandible, both active and passive, was limited. Flexion of the head on the thorax was limited by the mandibular and cervical swellings. The clavicles were enlarged to palpation. No abnormalities

were detected in other parts of the body. On the day of admission the temperature fluctuated between 100 and 101° F. The tuberculin skin test was negative.

The hemoglobin was reduced to 8.6 Gm. per 100 c.c. (59 per cent); the red cells were reduced to 2.9 million per cubic millimeter. There were 13,000 leucocytes per cubic millimeter; 60 per cent polymorphonuclears, 25 per cent lymphocytes, 12 per cent monocytes, and 3 per cent eosinophiles. Kline's test on the serum gave a nonsyphilitic reaction. There were no cold agglutinins in the blood. Sedimentation rate of the red cells was 142 mm. at the end of one hour. The Rh factor was present and the blood group was A. Agglutination tests on the serum were negative for the following organisms: *Eberthella typhosa* H and O; *Shigella dysenteriae* Flexner (group), *Shigella sonnei, Salmonella paratyphi B, Salmonella enteritidis, Salmonella choleraesuis,* and *Salmonella typhimurium; Brucella abortus.*

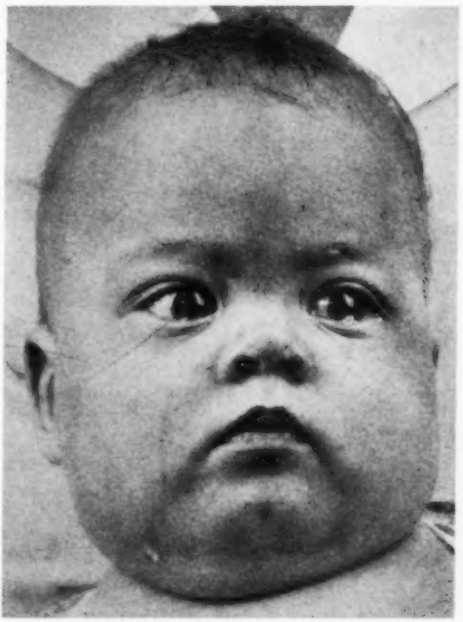


Fig. 1A.—Case 1. Facial swellings one month after their appearance.

The serum phosphorus was 6.8 mg. per 100 c.c., the serum calcium was not obtained; there were 15.0 units (Bodansky) of phosphatase per 100 c.c. of blood serum.

Roentgenograms of the entire skeleton disclosed scattered cortical thickenings in the following bones (Fig. 1*B*); mandible, both clavicles, and both ulnas. Later a small thickening appeared in the cortex of the right radius. The ribs were not affected and there was no evidence of pleural exudate as in three of the earlier patients.[2]

A block of bone was removed from the thickened right clavicle. At the operation the periosteum was swollen markedly. The microscopic section showed hyperplasia of the cortex under an actively proliferating periosteum; there were, however, no signs of inflammation or subperiosteal bleeding. Aerobic and anaerobic cultures from the right clavicle yielded no bacteria. Virus studies on the same material have not been concluded.

During the first week of hospital residence a mild fever was present; the maximal daily temperature varied between 100 and 101.5° F. During the second and third weeks there was no fever. The swellings in the face began to diminish during the second hospital week.

The infant was normally active and happy in the hospital. At the end of three weeks the facial swellings were small but still visible; they disappeared completely later at home. Her family physician reports that she has remained asymptomatic without recurrence of the facial swellings during eight months at home.

The mandibular findings in the roentgenogram (Fig. 1*C*) changed very little with the passing of time in contrast to the rapid fluctuations of the clavicular and ulnar thickenings (Fig. 1*D*).

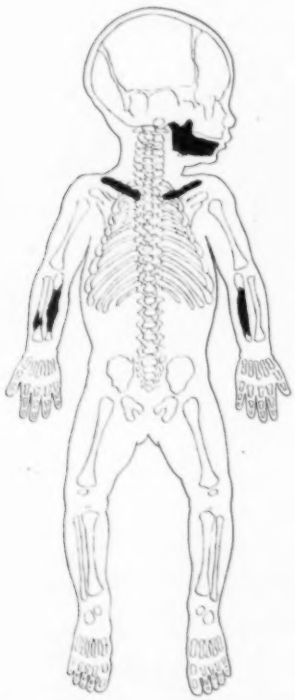


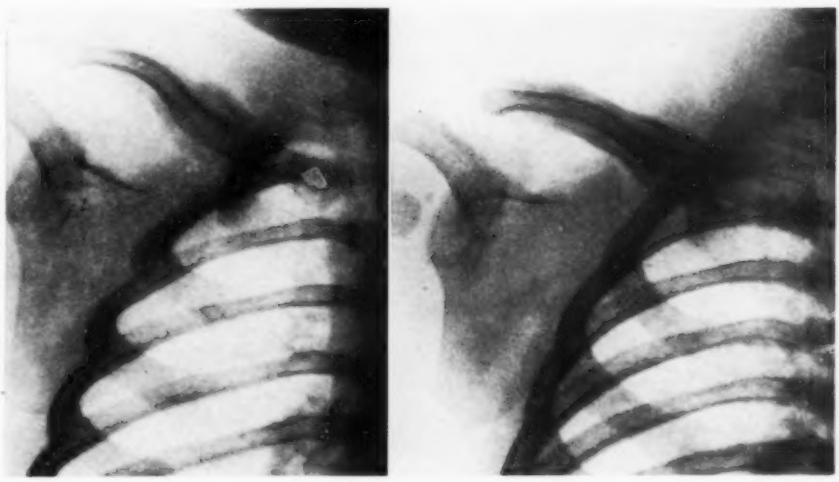
Fig. 1*B*.—Case 1. Diagram of the skeleton showing the scattered cortical thickenings in the mandible, both clavicles, both ulnas, and the right radius.

CASE 2.—A. M., a white female, was first seen when she was 27 months of age with the complaint of pain in the legs which had been present for seven months. She was normal at birth and thrived during the first year on a normal diet. She had had an adequate amount of Vitamin C which had been taken daily since the early weeks of life; Vitamin D had also been taken regularly in adequate amounts.

She had no complaints until the eighteenth month when she became "fussy" and lost her appetite. Hyperirritability and anorexia persisted until the twentieth month when tender hard swellings appeared over the left tibia and in the dorsum of the left foot. There was no redness in the swellings but the overlying skin was shiny. After a few days the swellings became so large and tender that she could not walk or wear shoes. After the first week the swellings diminished somewhat in size and the tenderness was not so marked; her appetite improved at the same time. During the twenty-third month excessive sweating at

night was observed at home and casts and albumin were found in the urine. Urethrotrigonitis was diagnosed after cystoscopic examination. During the twenty-sixth month anorexia became more marked and the left leg became swollen, tender, and shiny for a second time.

Fig. 1*C*.—Case 1. Roentgenogram of the mandible in left lateral oblique projection showing swelling, cortical thickening, and sclerosis of the left side of the mandible.



1. *2.*

Fig. 1*D*.—Case 1. Rapid, progressive sclerosis of the right clavicle. *1*, Five weeks after onset the clavicle is partially covered by a shadow which approximates water density. *2*, Six weeks after onset, the clavicle is now completely enveloped in a heavy bony shell of calcium density. One month later, in a film not shown here, the cortical thickening was reduced to paper thinness.

Fever had never been observed and there were no facial swellings as in Case 1. At twenty-seven months the only significant finding in the physical examination was a firm swelling of the left leg below the knee with tenderness of the left tibia. The swelling extended into the

dorsum of the foot; there was no hyperemia or edema. The temperature was 100° F. the first day and 100.5° F. the second day, but it remained below 100° during the remainder of a hospital residence of twenty days.

The red blood cells were normal in number and contained a normal amount of hemoglobin. There were 12,000 leucocytes per cubic millimeter; 59 per cent polymorphonuclears, 39 per cent lymphocytes, and 2 per cent monocytes. The sedimentation rate of the erythrocytes was 22 mm. at the end of one hour. The urine was normal chemically and cytologically.

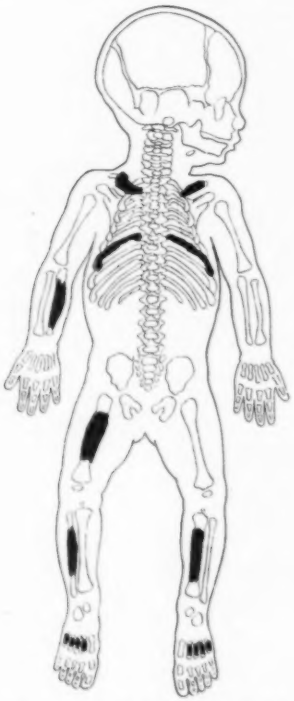


Fig. 2*A*.—Case 2. Diagram of the skeleton showing scattered hyperostoses in both clavicles, the right and left seventh ribs, right ulna, right femur, right fibula, left tibia, and several metatarsals in both feet. The mandible was not affected.

Phosphorus, calcium, and phosphatase were present in normal amounts in the blood serum. The blood proteins were present in normal amounts and in normal proportions. The prothrombin time was 20.3 seconds.

Culture of the blood yielded no growth and Kline's test gave a nonsyphilitic reaction. Agglutination tests for the following bacteria were negative; *Eberthella typhosa* H and O; *Shigella dysenteriae* Flexner (group), *Shigella sonnei*, *Salmonella paratyphi B*, *Salmonella enteritidis*, *Salmonella choleraesuis*, and *Salmonella typhimurium*; *Brucella abortus*.

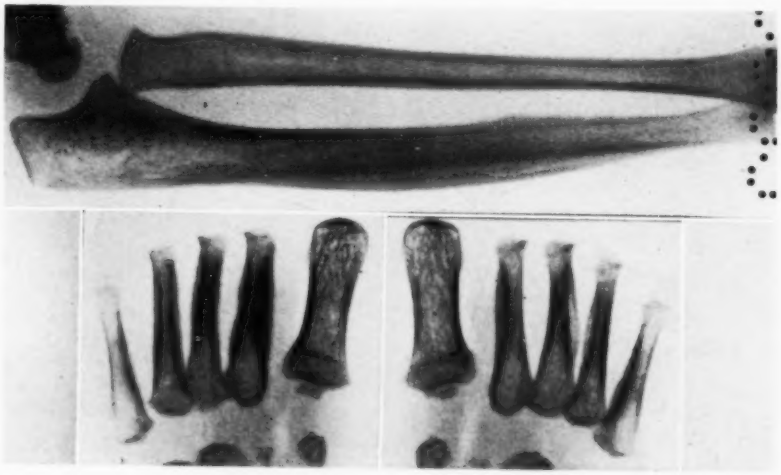
Kajdi's Vitamin C tolerance test gave an index of 6.0 which was interpreted to indicate a low reserve of Vitamin C.

Roentgenograms of the entire skeleton were made and cortical hyperostoses were found in both clavicles, the right and left seventh ribs, the right ulna, right femur, right fibula, left tibia and the metatarsals in both feet (Fig. 2*A*). The cortical thickenings in the left clavicle, the ulna, tibia and femur were all lamellated (Fig. 2*B*, *1*). Lamellation has not been found in the proved early stages of bone lesions in any patient and its presence probably indicates

a longstanding bone disease. The second, third, fourth, and fifth metatarsals in both feet were thickened; the first metatarsals in contrast were normal (Fig. 2B, *2*).

The patient began to improve a few days after admission to the hospital. As the pain in her legs and feet diminished, she became more active. When she was discharged after twenty-two days, she was walking and eating normally. Roentgen examination at 29 months of age showed all the bone lesions to be still present and not significantly changed. The patient is now well at home and has been asymptomatic during one year since discharge from the hospital.

1.



2.

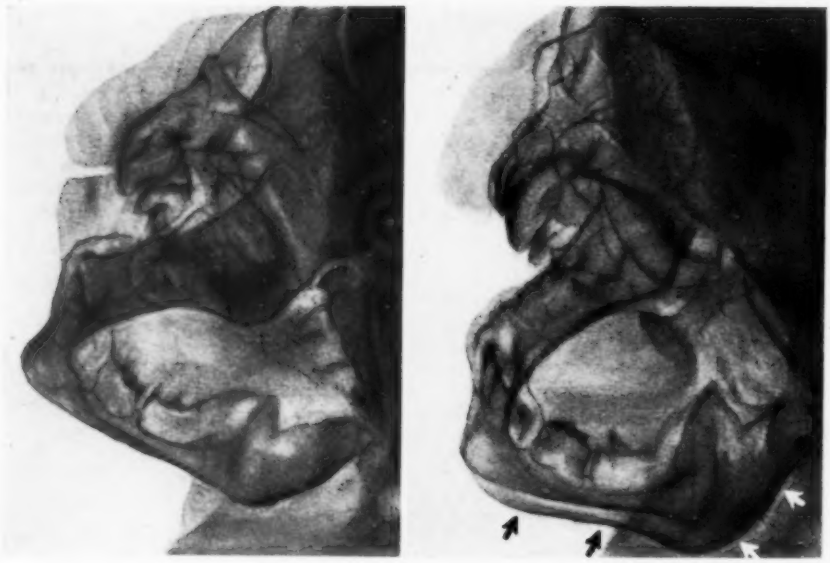
Fig. 2*B*.—Case 2. *1*, Lamellated thickening of the cortex of the right ulna. *2*, Symmetrical cortical thickenings in the second, third, fourth, and fifth metatarsals of both feet. The first metatarsals, in contrast, are not involved. The phalanges were normal.

Case 3.—W. O., a white male, was a patient of Dr. Richard Kegel of Cooperstown, N. Y., who kindly provided the clinical data and the roentgenograms for this report. The infant was born of a healthy mother after a normal gestation; the birth weight was 7 pounds. A cleft in the soft palate was identified during the neonatal period. Breast feeding was discontinued after two days and he was given a cow's milk formula with adequate Vitamin D and orange juice daily.

During the first six weeks he thrived; he had been taking 1 ounce of fresh orange juice and 4 drops of Navitol (Vitamin D) each day. When 6 weeks of age he was 23 inches in length and weighed 8 pounds, 4 ounces.

At 7 weeks, without premonitory symptoms, a large swelling suddenly appeared in the left cheek. Examination disclosed a poorly defined lump in the left cheek, most marked near the ramus and angle of the mandible. This mass did not seem to be painful or tender and was not discolored or excessively warm. The rectal temperature was 98.8° F. There were 21,000 leucocytes per cubic millimeter; 53 per cent polymorphonuclears, 42 per cent lymphocytes, 3 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. Roentgen examination of the mandible at this time showed a soft tissue swelling in the submaxillary region but the mandible itself was normal. Sulfadiazine was given for seven days without noticeable effect on the facial swelling.

At 9 weeks of age, two weeks after the onset, the facial swelling on the left side began to increase in size and a new swelling appeared suddenly in the right cheek. At this time there were 11,100 leucocytes per cubic millimeter; 46 per cent polymorphonuclears, 51 per cent



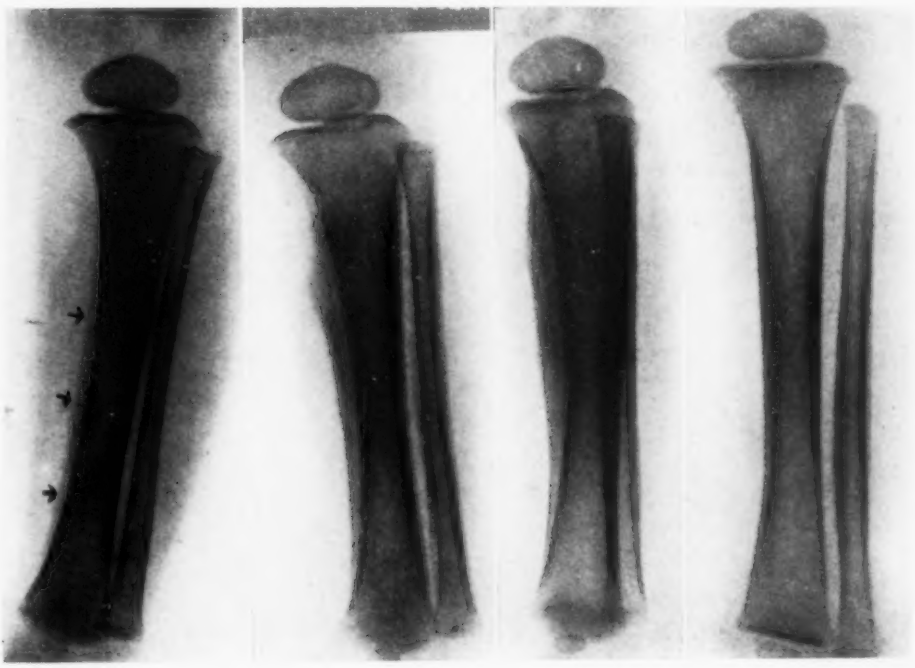
1. *2.*

Fig. 3*A*.—Case 3. *1*, The left side of the mandible is normal roentgenographically, although a soft tissue swelling under the mandible was visible in the original film. *2*, The same projection of the mandible at 11 weeks of age; cortical thickening on the underside of the mandible is now clearly visible (arrow). (Drawings of roentgenograms.)

Fig. 3*B*.—Case 3. Photograph of the facial swellings at 12 weeks of age, five weeks after the appearance of the swelling on the left side and three weeks after the appearance of the swelling on the right.

lymphocytes, and 3 per cent monocytes. At eleven weeks the right and left facial swellings were approximately the same size; roentgenograms at this time showed a distinct cortical thickening of the left side of the mandible (Fig. 3*A*). At twelve weeks the facial swellings were still conspicuous (Fig. 3*B*).

Despite the persistence of these swellings there were no associated constitutional or local symptoms and the infant continued to thrive. The patient remained afebrile. At the end of three months he weighed 11 pounds and was 25 inches in length. At 5 months he weighed 14 pounds.



1. *2.* *3.* *4.*

Fig. 4*A*.—Case 4. Progressive changes in the left tibia and fibula from the third to the fourteenth week after onset. *1*, Three weeks after onset the medial side of the tibia is covered with a faint, short, thin strip of water density (arrows). *2*, Five weeks after onset the tibia and fibula are surrounded by long, thick, sclerotic envelopes of calcium density. *3*, Eight weeks after onset the cortical thickenings have increased in depth and density. The medial surface of the hyperostosis is now rough. *4*, Fourteen weeks after onset the hyperostoses are shrunken in comparison with earlier findings. The absence of metaphyseal and epiphyseal changes suggestive of scurvy at all stages is noteworthy. There is a striking absence of transverse lines in these last films.

At 4 months, films of the entire skeleton were made and no abnormalities were disclosed save for the mandibular thickening which now appeared lamellated. The entire skeleton was examined again roentgenographically at 9 months and appeared normal excepting the mandible. By this time the swelling on the right side of the face had disappeared and that on the left side was visible but much smaller than in the earlier examinations. Fever was not observed during these later months of observation.

CASE 4.—A. S. was a patient of Dr. Bruce Chown of Winnipeg, Canada, who kindly provided the clinical data and the roentgenograms for this report. She was born of a healthy mother after a normal gestation. During the first four months she grew and developed nor-

mally. Then, after a fretful night, her face was found to be swollen in the morning; there were no precursory symptoms. The next day her goins and legs were tender and her temperature ranged between 100 and 102° F. The fever and facial swelling persisted during the following three weeks when she was admitted to the Children's Hospital at Winnipeg.

On admission there she weighed 14 pounds and had a temperature of 101° F. The nutritional state was good but a moderate pallor was present. "The right side of the face was swollen from the ear forward to the maxillary prominence and from the temporal region downward to the inframandibular region." This swelling was firm; the skin overlying it was shiny but not discolored. The buccal mucosa internal to the swelling was normal. The right leg was diffusely swollen and shiny; the left leg was normal. Wassermann's test on the blood serum gave a nonsyphilitic reaction.

Fig. 4*B*.—Case 4. Massive symmetrical cortical hyperostosis of the ulnas eight weeks after onset. The radii in contrast are not affected.

Roentgenograms made at admission (three weeks after onset) showed indefinite thickenings of the shafts of the long bones which contained very little calcium (Fig. 4*A*). In later films (Figs. 4*A* and 4*B*), denser and thicker cortical thickenings appeared and then after a few weeks began to regress. Films were not made of the head or thorax so that the status of the mandible, the clavicles, and the ribs was never determined. In view of the fact that the mandibles were thickened in all other patients who exhibited facial swellings, it is probable that the mandible of this patient who had facial swellings was also thickened in the same fashion, although it was not demonstrated. The distribution of the hyperostoses in the extremities is shown in Fig. 4*C*.

In the hospital large doses of orange juice were given because of the possibility that the bone lesions were due to a deficiency of Vitamin C. During the first two weeks of this treatment there was some diminution in the size of the facial swellings but on the fifteenth day after admission (five weeks after onset) the swellings on the right side suddenly began to increase in size and at the same time a new swelling suddenly appeared in the left cheek. During the following seven days the swellings subsided but suddenly recurred again after three

weeks notwithstanding the daily intake of large amounts of orange juice. She remained in the hospital for seven additional weeks until sixteen weeks after the onset. A daily fever varying between 99 and 101° F. persisted until discharge from the hospital; otherwise she was without symptoms.

CASE 5.—P. F. was a patient of Dr. Clement Smith of Detroit to whom I am indebted for the clinical data and roentgenograms in this report. At 22 months of age this boy was admitted to the Children's Hospital of Michigan with the complaints of aching joints, refusal to walk, and recurrent fever of six weeks' duration. He was born after a normal gestation by spontaneous delivery; the mother's serologic tests for syphilis were negative during the pregnancy. The birth weight was 6 pounds. He was breast fed during the first six weeks and then given an evaporated milk formula. Cod-liver oil and orange juice were started a few days after birth. The orange juice was taken well; for several months prior to the onset of this illness 2 ounces of orange juice had been ingested daily.

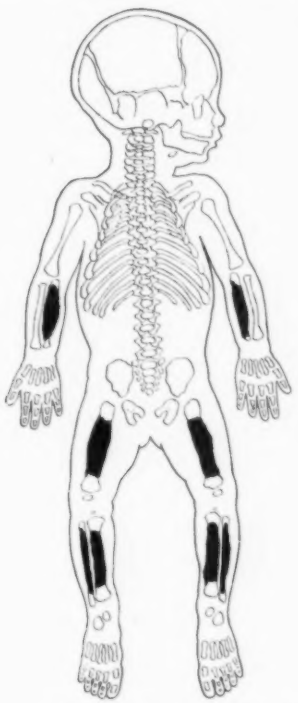


Fig. 4*C*.—Case 4. Diagram of the skeleton showing the distribution of the cortical hyperostoses in the extremities. The head and thorax were not examined roentgenographically and the status of the mandible, clavicles, scapulas, and ribs was not determined.

He was healthy until six weeks before admission, when he became listless and inactive if left alone but was hyperirritable and nervous when disturbed. The legs and arms were painful during movement and tender on manipulation; he cried when he was picked up. He seemed to be feverish at home, but the temperature was not measured. Rheumatic fever was suspected by his physician.

On admission he was found to be well nourished but very irritable. All of the long bones in the extremities were tender to pressure. Motion at the joints was free and no

periarticular swellings were observed. There were no facial swellings. No significant positive findings were revealed in the hospital other than the roentgen changes. The urine was normal microscopically and chemically. The hemoglobin measured 80 per cent; there were 14,000 leucocytes per cubic millimeter; polymorphonuclears 51 per cent; lymphocytes 49 per cent. The skin did not react to tuberculin, and Kahn's test on the blood gave a nonsyphilitic reaction. There were 6.1 mg. of phosphorus per 100 c.c. of serum, and 10.7 mg. of calcium. The serum phosphatase equaled 10.7 Bodansky units per 100 c.c.

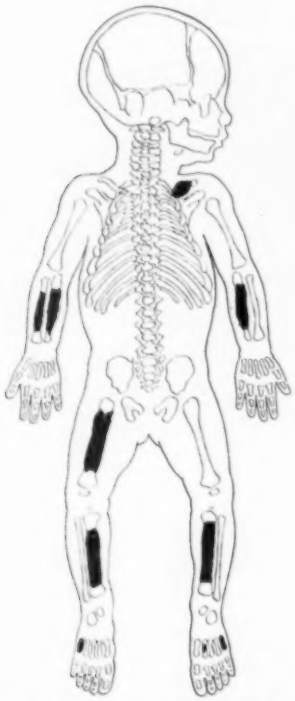


Fig. 5A.—Case 5. Diagram of the skeleton showing the distribution of cortical hyperostoses. The head was never examined roentgenographically.

Roentgenograms of the thorax, pelvis, and extremities disclosed multiple cortical hyperostoses scattered in the left clavicle, both ulnas, left radius, right femur, both tibias, and three metatarsals (Fig. 5*A*). The changes were pronounced in both ulnas (Fig. 5*B*, *1*) and barely perceptible in the left radius and absent in the right radius. Both of the fifth metatarsals exhibited massive cortical thickenings (Fig. 5*B*, *2*); the remainder of the metatarsals were unaffected save the second left metatarsal which showed slight thickening of the medial segment of its cortex. The phalanges were normal in the hands and the feet; the metacarpals were not involved. All of the affected bones were free of scorbutic changes in the metaphyses and in the epiphyseal ossification centers.

In a specimen of bone removed from the tibia, hyperplasia of the cortex under the periosteum was found; there was no inflammatory cellular infiltration and no evidence of subperiosteal hemorrhage.

During a residence of two weeks in the hospital the tenderness in the extremities gradually subsided and the patient was asymptomatic at the time of discharge.

CASE 6.—A. L., a white male 3 months of age, was admitted to the Charles V. Chapin Hospital in Providence, R. I. (data through the courtesy of Dr. Richard K. Whipple) with a chief complaint of swelling of the right side of the face for five days. Prior to the present illness, the infant had thrived since his birth on Jan. 25, 1946. The delivery was normal and

1.

2.

Fig. 5*B*.—Case 5. 1, Long, thick hyperostosis in the left ulna. The ulnar side of the radius is also slightly thickened. *2*, Symmetrical hyperostoses in the fifth metatarsals. There is also some cortical thickening on the medial side of the second left metatarsal.

the birth weight was 8 pounds. At the time of admission he was on a three-hour feeding schedule which included the daily intake of 2 teaspoons of cereal, 1 ounce of orange juice and cod-liver oil in unstated quantities. No allergic reactions had been noted; immunizing agents had not been administered. There were eight siblings in the family, all in good health.

The initial finding in this illness was detected nine days before admission when the mother noted that the right side of the face was tender. Three or four days later a swelling appeared in the site of the tenderness. The swelling gradually enlarged until admission. Food was taken by mouth without difficulty, but the infant vomited occasionally.

Fig. 6A.—Case 6. *1*, Cortical hyperostosis of the left parietal bone. Similar changes were demonstrated in the right parietal bone. *2*, Thickening and sclerosis of the right side of the mandible five days after swelling was first detected in the soft tissues in the right side of the jaw. *3*, Massive hyperostosis of the mandible twenty-seven days after *2*.

At admission the only positive physical finding was the firm, tender swelling of the right side of the face and jaw which seemed to be attached to the mandible. Examination of the blood disclosed that hemoglobin was 68 per cent and that there were 4.7 million erythrocytes per cubic millimeter, and 24,000 leucocytes. The findings in the urine and spinal fluid were normal. The admission roentgenograms revealed thickenings and sclerosis of the right side of the mandible; the body, ramus, coronoid, and articular processes were all affected (Figs. 6*A*, *2* and *3*).

At the time of writing, the patient had been under observation in the hospital for five weeks. Fever was present on admission and has continued intermittently, reaching maximal levels of 102.5° F. The right-sided facial swelling became larger during the first hospital week; at the end of this first week a firm swelling appeared in the left side of the face. Two weeks after admission a swelling was noted in the scalp, on the right side; at the same time the conjunctiva and lids of the right eye became swollen. Then a swelling appeared in the scalp in the left posterior parietal region. Roentgenograms of the head showed symmetrical external thickenings of the parietal bones (Fig. 6*A*, *1*). During the second and third hospital weeks, 2,700,000 units of penicillin were administered; during the fourth week he received 10 Gm. sulfadiazine. The fever and swellings were apparently not altered by either of these drugs. Five weeks after admission a swelling of the soft tissues was noted in the right sternoclavicular region and roentgenograms disclosed massive cortical thickening of the right clavicle. At the time of the last observation, hyperostoses had been demonstrated in both parietal bones, the mandible, and the right clavicle (Fig. 6*B*). No abnormalities were visualized in the ribs, scapulas, or bones of the extremities.

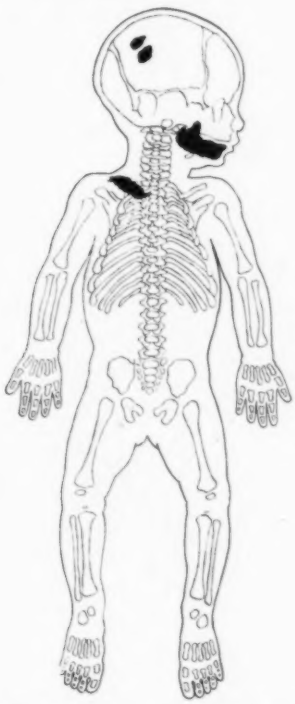


Fig. 6*B*.—Case 6. Diagram of the distribution of multiple hyperostoses in the right and left parietal bones, in the mandible, and in the right clavicle.

An anemia developed and was most marked in the third hospital week when the hemoglobin approximated 50 per cent and the erythrocytes numbered 3.9 million per cubic millimeter. A transfusion of 120 c.c. of blood was given. The number of leucocytes varied from 29,000 to 7,000 per cubic millimeter; the polymorphonuclears from 60 to 35 per cent, and the lymphocytes from 47 to 36 per cent. On two occasions the monocytes comprised 10 per cent of the total number of leucocytes. There was no eosinophilia. The Wassermann

and Hinton blood tests gave nonsyphilitic reactions. The tuberculin skin test was negative. Blood cultures were sterile. The concentration of calcium and phosphate in the blood serum was normal. Excretory urography was abandoned owing to positive cutaneous reactions to diodrast and skiodan.

COMMENT

The study of six additional cases supports the view that infantile cortical hyperostoses represent a disease which until recently has not been recognized as a clinical or roentgenographic or anatomic entity. The essential skeletal change has again been demonstrated to be subperiosteal cortical hyperostosis causing external thickening of the bone. The cause and pathogenesis of the disorder remain undetermined. Bacterial infections, scurvy, and rickets, trauma, and neoplastic disease all appear to be satisfactorily excluded as causal agents. Virus infection and allergic reactions have not been demonstrated or disproved.

As was to be expected, several new features were disclosed by the investigation of more patients; both the clinical and roentgen pictures are more variable than previously described. It is now evident that the onset may occur later than the third month of life; initial symptoms may appear during the second year (eighteenth month in Case 2 and twentieth month in Case 5). The duration of the active manifestations varied from eight weeks in Case 5 to nine months in Case 2. The uneven course of the disease was again well demonstrated in the recurrences and the remissions of the facial swellings in Case 4 and in the intermittent symptoms in Case 2.

In all cases the tender soft tissue swellings were deeply placed, showed no increase in local heat and were not visibly hyperemic. The subcutaneous fat overlying the swellings retained its normal radiolucency, the swellings appeared to be confined to the central shadow of the muscular masses which surround the bones of the extremities. It is noteworthy that facial swellings appeared in all patients with onset prior to the fifth month of life, but were present in neither of the patients with later ones (Cases 2 and 5). The scalp became swollen in Case 6, the first and only example of involvement of this part of the body. Later on, the conjunctiva and lids of this patient's right eye also became swollen. The nature of the soft tissue swellings and the tissue elements actually involved during the early phase of this disease are not known. In biopsies made several weeks after the onset of symptoms, Smyth and his co-workers[3] reported fibrosis, degeneration, and atrophy of the masseter muscle in one case, and degeneration with fatty and fibrous displacement of the intercostal muscles in another.

Five of our six patients exhibited fever. Fever in contrast was never detected in Case 3 although it was watched for carefully. The disease has now run its course in two patients without fever being recognized (see also Case 4 in reference 2). Two patients were moderately anemic, both had received sulfonamide therapy before the anemia was detected. In our first group of patients, two were anemic who had not received sulfonamides.

The most striking difference in the findings in our two groups was the absence of pleurisy in all of the six patients in the second group; in contrast,

three of the four infants in the first group showed roentgen signs of pleural exudate. It is to be remembered that pleurisy developed only in patients with extensive cortical thickenings in the ribs.

As in the first group, the number, distribution, and magnitude of the skeletal lesions varied greatly. The mandible alone was affected in Case 3. In contrast, neither facial swellings nor mandibular hyperostoses were observed in patients 2 and 5 who had the latest onsets during the second year. Mandibular and facial lesions were also absent in the two patients with late onsets described by Smyth and associates.[3] All of our patients who became ill prior to the sixth month have shown facial swellings (eight cases) and seven of these, all whose mandibles were examined roentgenographically, showed mandibular hyperostoses. This raises some doubt as to the validity of including the older patients in the same syndrome. We have included them because, save for the absence of mandibular involvement, they appear to be similar in all other important respects. Cortical thickenings of the metatarsals were demonstrated in both of the older patients, both of whom refused to walk at the onset of the disease. It is possible that trauma to the metatarsals incidental to walking and weight-bearing was partially responsible for the lesions in the metatarsals. The neighboring phalanges were not affected. We have not made roentgenograms of the feet in the younger infants; none of them have had swelling or tenderness of the feet. We have not demonstrated lesions in the hands in any patient.

The scapulas were not affected in any of these six patients. The ribs were thickened in only one infant (Case 2) and the costal changes were limited to the right and left seventh ribs. Clavicular hyperostosis was demonstrated in four cases, was absent in one (Case 3) and the clavicles were not examined roentgenographically in one (Case 4). The clavicles have been involved as frequently as the mandible, that is, in seven of nine patients who have had roentgenograms of the thorax. The ulnas appear to be considerably more vulnerable than the radii and may be markedly thickened when the radii appear to be normal (see Fig. 4*B*). We have not yet observed the converse. Fibular lesions may be present or absent when the tibias are affected, or fibular thickenings may develop in the absence of changes in the adjacent tibia. The bones of the calvarium have not been affected save in Case 6. I have, however, examined a patient in consultation, whose case is not reported here, who showed cortical thickenings in the edges of the frontal and parietal bones contiguous to the anterior fontanel in addition to thickenings of both clavicles and both ulnas.

Soft tissue swellings were evident clinically before cortical hyperostoses were visible roentgenographically in Cases 3 and 4. In the latter, tender swellings had been present in the leg for three weeks when the films showed no signs of excessive cortical bone in the tibia; two weeks later cortical thickening became visible and succeeding films showed an increase and then a regression of the tibial lesions. The lag in the appearance of the hyperostoses in roentgenograms must be taken into consideration in diagnosis. Successive films should be made for at least four weeks after the appearance of soft tissue swellings; absence of cortical hyperostoses during the first days after the onset is probably characteristic and is to be expected.

Although many and probably the principal clinical and roentgen features of this disorder have been revealed by the study of ten patients, many important questions remain unsolved. Observations at onset and during the early phases are unfortunately still meager. Biopsies of the soft tissue swellings and the skeletal lesions as well as bacterial and viral search during the first stage of the disease would probably throw much light on the cause and pathogenesis. Comprehensive investigation of allergic reactions early, near the onset, are essential before allergy can be evaluated properly as a causal agent. The favorable outcome in all cases has precluded necropsy.

In all patients the disease appears to have run its course unmodified by the therapeutic agents which have been used. Sulfonamides and penicillin have been equally ineffective in the few patients to whom they have been administered. Orange juice and ascorbic acid have failed conspicuously to cure or even prevent relapses. We plan to make the therapeutic trial with some of the new antiallergic drugs when the opportunity presents itself. There is no clinical evidence thus far that the disease is a contagious one; there have been no contact or sibling infections.

Infantile cortical hyperostoses can be readily confused with a number of conditions, especially if roentgenograms of the bones are not made or if they are made too early in the disease before the hyperostoses appear. The facial swellings have suggested the possibility of parotitis in some cases, as well as osteomyelitis of the mandible and neoplasm of the mandible. Swellings, tenderness, and painful pseudoparalysis of the extremities are all manifestations of scurvy. Fever, hyperirritability, and painful pseudoparalysis resemble some cases of poliomyelitis. Anemia, fever, and bone pain are a common complex of manifestations in many cases of infantile leucemia. Fever, pain, and tenderness in the extremities and increased sedimentation rate of the erythrocytes may point to rheumatoid arthritis or rheumatic fever; the latter was the admission diagnosis in Case 5. In active rheumatoid arthritis, regional cortical thickenings of the bones adjacent to the soft tissue swellings are not uncommon[4] and would be difficult to differentiate on roentgen grounds alone from the thickenings of the metatarsals demonstrated in Case 2. If and when satisfactory specimens of the soft tissue swellings become available, careful microscopic search should be made for tissue changes characteristic of the rheumatic and rheumatoid states.

SUMMARY

Six additional cases of infantile cortical hyperostoses are described. Ten cases have now been reported from this clinic. The findings indicate that this disorder is a new infantile syndrome for which the cause is unknown and the pathogenesis obscure.

The skeletal lesion is a hyperplasia of subperiosteal bone on the periphery of the cortex. Pleural exudate removed from one patient contained 500 monocytes per cubic millimeter. The nature of the soft tissue swellings and the tissue elements in them which are affected primarily have not been determined.

The components of the syndrome common to all patients are deep swellings of the soft tissues and cortical hyperostoses in the neighboring bones. Other important features lacking in some patients include fever, hyperirritability, pseudoparalysis, dysphagia, pleurisy, anemia, leucocytosis, monocytosis, increased rate of sedimentation of erythrocytes, and excessive serum phosphatase. Soft tissue swellings have been located in the scalp, face, neck, thorax, and extremities. Hyperostoses have been demonstrated in the calvarium, mandible, clavicles, scapulas, ribs and the tubular bones of the extremities including the metatarsals. The mandible and the clavicles are affected most frequently.

Initial symptoms have appeared as early as the third week of life and as late as the twentieth month. Duration of the active manifestations has varied from eight weeks to nine months. All patients have recovered. The course of the disease has not been modified by the administration of sulfonamides or penicillin.

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THE USE OF PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS IN CHILDREN

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EARLY reports on the use of penicillin in the treatment of subacute bacterial endocarditis have included histories of a small number of children. The outcome was favorable in every instance but one, in which the dosage employed was unusually small. Ten children less than 15 years of age whose endocarditis was caused by *Streptococcus viridans* have been described in sufficient detail in the literature to be included in this summary, and we have added four more whom we have observed.

Collins[1] treated a boy 10 years of age, who had congenital heart disease and bacterial endocarditis, with 1,400,000 units of penicillin administered intramuscularly over a period of fourteen days. The child recovered and remained well during a period of observation of six months. Among the twenty patients with subacute bacterial endocarditis treated by Dawson and Hunter,[2] one was a boy 13 years of age with an aortic and mitral valvulitis of rheumatic origin and a superimposed infection with *Str. viridans*. A total of 1,410,000 units of penicillin was administered by continuous intravenous drip over a period of twelve days together with heparin given by intramuscular injection. The blood stream became sterile and the patient remained well over a period of observation of six months. In a second report,[3] the same authors included the case of a 13-year-old girl with a congenital heart lesion, probably an interventricular septal defect, who developed a bacterial endocarditis due to one of the indifferent groups of streptococci. This patient was more refractory than their previous child and required a total of 34,400,000 units of penicillin before the symptoms subsided and the blood stream remained sterile. She recovered and remained well for a period of three months of observation. Since this infection was due to a streptococcus other than the viridans variety, the case history has not been included in the accompanying table (Table I).

Goerner and associates[4] reported the case of a boy 10 years of age who had a ventricular septal defect and bacterial endocarditis. This boy was one of the first patients treated with penicillin and he received only 240,000 units. He failed to recover. Two other children, 11 and 13 years of age, with the infection superimposed upon previous rheumatic infections, received much larger doses (9,120,000 and 4,900,000 units) and recovered. One was observed for twelve months and the other for six months and neither had further symptoms of the disease. The drug was administered by the continuous intravenous route and heparin was not used.

Among twenty patients reported by Flippin and associates[5] there were three children who were treated successfully. Their ages were 7, 10, and 12 years respectively. Two had congenital heart disease and the third had rheu-

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matic valvulitis. Each received 4,200,000 units administered by continuous intravenous drip over a period of fourteen days. No heparin was employed. They remained well for periods of observation ranging from thirteen to fifteen months.

Among the group of patients reported by Hirsh and Dowling[6] there was a girl 13 years of age with mitral and aortic valvulitis who had had symptoms of bacterial endocarditis for three months before treatment was started. She received 11,500,000 units of penicillin and recovered with no symptoms of the infection for a period of observation of four months.

Of special interest was the recovery of a child treated with penicillin administered orally. Burke and associates[7] observed a girl 11 years of age who had a ventricular septal defect and developed symptoms of subacute bacterial endocarditis four weeks before admission to the hospital. Blood cultures were positive for *Str. viridans* on three occasions. Penicillin was administered in doses of 100,000 units in double gelatin capsules every three hours. Two tablets of aluminum hydroxide were given from fifteen to thirty minutes before each dose. Blood levels of the drug varied from 0.078 to 1.24 units. A total of 11,200,000 units were administered during a fourteen-day period and the child recovered from the infection. She remained well for a four-month period of observation.

The four children of our series whose histories are reported here in detail had clinical evidence of subacute bacterial endocarditis and positive blood cultures for *Str. viridans*. Penicillin was administered by intermittent intramuscular injections, total dosage ranging from 6,000,000 to 8,500,000 units during periods of four to eight weeks. No heparin was employed. Recovery occurred in every instance and the patients have remained well for periods of one year or more.

CASE REPORTS

Summary of Case 1.—A white girl, 9 years of age, with a history of several attacks of rheumatic fever and a well-advanced mitral valvulitis suddenly developed acute symptoms of subacute bacterial endocarditis and embolism of an intracranial vessel. Treatment with 4,500,000 units over a period of eight weeks led to complete recovery from the bacterial endocarditis and the patient has remained well during a period of observation of eighteen months.

CASE 1.—This child had her first attack of rheumatic fever at the age of 5 years (1939). Several exacerbations of the disease occurred during the next two years and the cardiac signs at that time were suggestive of mitral stenosis. In the autumn of 1943 she was included in a group of children who received daily doses of 1.0 Gm. of sulfathiazole for the prevention of recurrences of rheumatic fever. She remained well throughout the year and in May, 1944, the treatment was discontinued.

Sept. 27, 1944, the child began to vomit, and a few hours later she became unconscious. No previous symptoms had been noted by the parents. When admitted to the hospital on September 28, she was still unconscious, had a fever of 102° F. and a few petechiae on the neck and in the sclera of one eye. The pulse was rapid, the heart enlarged, and there was a loud systolic murmur over the entire precordium. The spleen was large. The Kernig and Brudzinski signs were positive and the neck was rigid.

At this time the hemoglobin value was 14 Gm. per cent and there were 42,400 white cells per cubic millimeter, of which 92 per cent were polymorphonuclear leucocytes. The urine was negative. In cultures of the nose and throat secretions were hemolytic streptococcus and hemolytic *Staphylococcus aureus*. Blood cultures were sterile. The cerebrospinal fluid contained: 360 cells, the majority of which were polymorphonuclear leucocytes; 30 mg. per cent of protein; 694 mg. per cent of chlorides; and 54 mg. per cent of sugar. On the following day the cerebrospinal fluid contained 100 cells and the Pandy reaction was negative.

On the suspicion that the child had a meningococcemia with an early meningitis, sulfadiazine and penicillin were administered and during the next five days the patient improved rapidly and medication was discontinued.

On Oct. 15, 1944 (eighteen days after admission), the child's temperature rose to 103° F. and petechiae appeared on the cheeks and trunk. The spleen was large and tender. Sulfadiazine was administered once more, but the crops of petechiae continued to appear during the following few days. Four blood cultures taken on different days were all negative.

By November 1 (thirty-two days after admission), the child had improved considerably, but at this time a blood culture showed twenty-four colonies of *Str. viridans* per cubic centimeter. This organism was found to be sensitive to penicillin. Treatment consisted of the intramuscular injection of 10,000 units of penicillin every three hours for a period of twenty-five days when a total of 2,000,000 units had been administered. Sulfadiazine, which was administered simultaneously in oral doses of 10 grains every four hours, produced blood levels varying from 3.2 to 8.0 mg. per cent.

On December 2, a second course of 2,500,000 units of penicillin was instituted. Transfusions of whole blood were given on two occasions during the course of the illness.

All symptoms of acute illness had disappeared and seven consecutive blood cultures were negative within three weeks after intensive penicillin therapy had been started. The child was discharged Dec. 30, 1944, to a convalescent home where she has remained well for the period of observation of eighteen months.

Summary of Case 2.—A Negro boy, 12 years of age, with aortic insufficiency of rheumatic origin, developed mild symptoms of subacute bacterial endocarditis. Treatment with 6,800,000 units of penicillin over a period of thirty-eight days resulted in complete recovery from the bacterial infection and he has remained well for a period of observation of sixteen months.

CASE 2.—This boy had an attack of rheumatic fever at 10 years of age (1942). It is possible that he had had previous attacks, but the history was uncertain. A diagnosis of insufficiency of the aortic valve was made in 1942 and the child was referred to the Condon School for crippled children. On Nov. 11, 1944, while attending this school, he was included in the series of children who started taking sulfadiazine in doses of 7.5 grains daily as a measure to prevent recurrences of rheumatic fever. During the next few months, he developed no symptoms of rheumatic fever although he had several colds. On several occasions it was noticed that he was steadily losing weight, and by February, 1945, he had lost a total of 9 pounds. He had no fever during school hours and the routine urinalyses and leucocyte counts were normal. He gave a history of profuse sweating at night.

He was admitted to the hospital Feb. 12, 1945, for more complete study. For the first time, areas of tenderness were noted on the dorsum of the left foot and in the distal phalanx of the little finger of the right hand. The tenderness could be detected by pressure over the small bones rather than by motion of the joints. The spleen was palpable but not greatly enlarged. The heart was enlarged and a blowing diastolic murmur was prominent at the base. A soft systolic murmur also occurred at the apical area. The blood pressure was 130 systolic and 50 diastolic. Shortly after he was admitted to the hospital, he developed hemorrhagic areas in the sclera.

The laboratory tests included a leucocyte count of 5,000 per cubic millimeter, a hemoglobin value of 8.5 Gm. per cent and an erythrocytic sedimentation rate of 27 mm. per hour.

The Kahn reaction was negative. Roentgenograms of the chest demonstrated the enlargement of the heart with a maximum width of 12.5 cm. in a chest 22.5 cm. wide. Electrocardiograms demonstrated some abnormalities of shape of the S-T segments and depression of T waves in the second and third leads, findings often associated with myocardial damage.

The patient was treated with aspirin on admission because he seemed to have an exacerbation of rheumatic fever. However, four specimens of blood taken during the first week of his hospitalization all contained *Str. viridans* and penicillin therapy was instituted in dosage of 25,000 units administered intramuscularly every three hours.

He received a total of 6,800,000 units of penicillin during a period of thirty-eight days. Sulfadiazine in oral doses of 15 grains every four hours was likewise given. All symptoms promptly subsided and he began to gain weight. The hemoglobin content of his blood rose to 12 Gm. per cent and fourteen blood samples taken during the next two months were sterile. He has been observed frequently since his dismissal from the hospital sixteen months ago and has remained well.

Summary of Case 3.—A Negro girl, 8 years of age, with a congenital cardiac lesion believed to be a defect of the interventricular septum, developed mild symptoms of subacute bacterial endocarditis. She received 7,000,000 units of penicillin over a period of thirty-five days and made a complete recovery. She has remained well for a period of observation of fourteen months.

CASE 3.—This Negro girl was first seen in the cardiac clinic when she was 6 years of age (1943). At this time she had a rough systolic murmur at the left of the sternum in the third and fourth intercostal spaces. The heart was not enlarged and the electrocardiogram showed a P-R interval of 0.20 seconds. The spleen was not palpable. A Kahn test of the blood was questionably positive at this time, but was subsequently negative. No antisyphilitic treatment was given.

At a routine visit to the cardiac clinic on March 3, 1945, she had vague symptoms of abdominal pain. No tenderness or rigidity of the abdomen could be detected but the spleen and liver were both two fingerbreadths below the costal margin. Petechiae were observed on the left shoulder and on the thighs. The cardiac signs were the same as noted previously except that a short systolic thrill could now be detected at the left sternal border at the level of the fourth intercostal space. She had no fever or other symptoms. She was admitted to the hospital March 3, 1945, and initial blood culture, reported on March 8, contained *Str. viridans.* No other positive blood cultures were obtained, but this single positive culture together with the clinical signs of bacterial endocarditis seemed to warrant the immediate institution of therapy. Penicillin was administered every three hours in doses of 25,000 units intramuscularly for a period of thirty-five days until a total dosage of 7,000,000 units had been given. The dosage of sulfadiazine for the first four days was 7.5 grains every four hours and was reduced to 7.5 grains twice a day thereafter. The child made a complete recovery. No more petechia appeared and the spleen became smaller. Twelve blood cultures were negative.

Shortly after her discharge from the hospital on May 19, 1945, she developed fever and loss of appetite. The spleen could again be palpated about one fingerbreadth below the costal margin. Readmitted to the hospital, she improved rapidly. Repeated blood cultures were negative and no treatment was given. She has been observed frequently in clinic during the fifteen months since that time and has been entirely well, except for the original congenital cardiac lesion.

Summary of Case 4.—A white boy, 11 years of age, with mitral valvulitis of rheumatic origin, developed acute symptoms of subacute bacterial endocarditis. Following the administration of 8,500,000 units of penicillin, complete recovery took place. Four months later, when his tonsils and adenoids were

TABLE I. CHILDREN WITH SUBACUTE

AUTHOR	AGE (YR.)	SEX	CARDIAC LESION	DURATION OF SYMPTOMS OF ENDOCARDITIS BEFORE TREATMENT	TOTAL DOSAGE OF PENICILLIN
1. Collins[1]	10	M	Congenital	6 weeks	1,400,000
2. Dawson and Hunter[2]	13	M	Rheumatic; aortic and mitral valvulitis	3 months	1,410,000
3. Goerner and others[4]	10	F	Congenital; ventricular septal defect	1 month	240,000
4. Goerner and others[4]	13	F	Rheumatic; mitral valvulitis	5 months	9,120,000
5. Goerner and others[4]	11	F	Rheumatic; mitral valvulitis	6 weeks	5,200,000
6. Flippin and others[5]	10	F	Congenital	6 weeks	4,200,000
7. Flippin and others[5]	12	F	Rheumatic	16 weeks	4,200,000
8. Flippin and others[5]	7	M	Congenital	12 weeks	4,200,000
9. Hirsh and Dowling[6]	13	F	Rheumatic; mitral and aortic valvulitis	3 months	11,200,000
10. Burke and others[7]	11	F	Congenital; ventricular septal defect	4 weeks	11,200,000
11. Lyon	9	F	Rheumatic; mitral valvulitis	5 weeks	4,500,000
12. Lyon	12	M	Rheumatic; aortic valvulitis	3 months	6,800,000
13. Lyon	8	F	Congenital; ventricular septal defect	1 week	7,000,000
14. Lyon	11	M	Rheumatic; mitral valvulitis	3 weeks	8,560,000

removed, an additional 800,000 units of penicillin were given and no recurrence of the bacterial endocarditis took place. When observed a year after his initial attack of bacterial endocarditis, he was in good health.

CASE 4.—(This boy is a patient of Dr. Frank Seinsheimer and we are grateful for his permission to include this report.) In the Autumn of 1944 this boy, then 10 years of age, had an attack of acute rheumatic fever. Six months later, in the second week of May, 1945, he developed fever and anorexia, and petechiae on the legs shortly afterward. *Str. viridans* was discovered in a blood culture and penicillin therapy was instituted.

He was referred to Dr. Seinsheimer and admitted to Cincinnati Children's Hospital June 9, 1945. He appeared weak and pale but no petechiae were visible until the third day, when showers of them appeared on the chest and arms. The spleen was palpable but not greatly enlarged. A loud, blowing, systolic murmur was audible over the apical area of the heart and was transmitted to the entire left chest and axilla. Roentgenograms demonstrated no cardiac enlargement and an electrocardiogram was normal. The hemoglobin content of the blood was 9.0 Gm. per cent and there were 9300 leucocytes per cubic millimeter, of which 67 per cent were polymorphonuclear leucocytes. Blood cultures on the first and third hospital days were positive for *Str. viridans.*

Penicillin had been administered for six days before the patient was admitted to the hospital, and the total amount was not known. The drug was instituted again on June 11, 1945, in doses of 20,000 units intramuscularly every four hours, and then increased two days later to 35,000 units every three hours. During a period of thirty days, a total of 8,560,000 units were given. Transfusions of 250 c.c. of whole blood were given on three occasions.

On the seventh hospital day (June 18) the patient experienced a sharp pain in the left lower quadrant of the abdomen and tenderness was noted in the left flank. These symptoms disappeared after a few hours and recovery was otherwise normal. The urine was negative at all times except for an occasional trace of albumin. The hemoglobin levels rose to 15 Gm. per cent by the end of the month and the sedimentation rates which were slightly elevated on admission (0.63 mm. per minute) fell to normal (0.30 mm. per minute). The blood became

BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN

DURATION OF THERAPY (DAYS)	METHOD OF ADMINISTRATION	OUTCOME	PERIOD OF OBSERVATION AFTER TREATMENT (MO.)
14	Intramuscular, intermittent, 12,500 units every 3 hours	Recovered	6
12	Intravenous, continuous drip, 120,000 units daily	Recovered	6
8	Intravenous, intermittent, 5,000 units every 4 hours	Died	
38	Intramuscular, intermittent, 20,000 units every 2 hours and later intravenous drip, 240,000 units daily	Recovered	12
27	Hypodermoclysis, continuous, 1,000,000 units total intravenous, continuous drip, 200,000 units daily	Recovered	6
14	Intravenous, continuous drip, 300,000 units daily	Recovered	15
14	Intravenous, continuous drip, 300,000 units daily	Recovered	14
14	Intravenous, continuous drip, 300,000 units daily	Recovered	13
56	Intramuscular, intermittent, 25,000-30,000 units every 2 hours	Recovered	4
14	Oral, 100,000 units every 3 hours	Recovered	4
57	Intramuscular, intermittent, 10,000 units every 3 hours	Recovered	18
34	Intramuscular, intermittent, 25,000 units every 3 hours	Recovered	16
35	Intramuscular, intermittent, 25,000 units every 3 hours	Recovered	15
30	Intramuscular, intermittent, 20,000 units every 4 hours then 35,000 units every 3 hours	Recovered	12

sterile eight days after the penicillin therapy had been started in the hospital and remained sterile on seven subsequent cultures.

On Nov. 13, 1945, about four months after recovery, the child's tonsils and adenoids were removed. During a period of about five days after the operation, penicillin was administered intramuscularly in doses of 20,000 units every three hours until a total of 800,000 units were given. Blood cultures at that time and a month later were negative and the child has been free from symptoms of bacterial endocarditis for a period of twelve months since the onset of illness.

COMMENT

Only one patient died and he had received only 240,000 units of penicillin. The others recovered without relapses or any evidence of vascular accidents after treatment was started. Children, in contrast with older patients, recuperate rapidly from acute infections and it is possible that endocardial lesions produced by the bacterial infection are less extensive in children and may be covered with epithelium rapidly after treatment is started. Likewise, the cardiac muscle of children may be able to withstand the strain of the infection or circulatory disturbance more readily than adults.

Dosage of 240,000 units proved inadequate. Two children of the group recovered after approximately one and a half million units had been given, but dosage varying from 4 to 11 million units was employed most frequently. It may be permissible to conclude at this time that not less than 1½ to 2 million units should be employed and that more will be required if the infection is severe or has been present for a long time, and if the patient's symptoms do not respond rapidly to the therapy. At least 200,000 units seems to be an adequate daily dose.

The method of administration of the drug seemed to be of little importance. Intermittent intramuscular injections were employed in our four patients and in two children reported previously. The child who received inadequate dosage and died likewise had the drug administered in this manner. The oral route was successful in one patient and in the remaining six children penicillin was given by continuous intravenous drip or by a combination of methods.

Other drugs do not seem to be necessary in the treatment of subacute bacterial endocarditis of children. Sulfonamides were employed in many of the early cases reported, including the first three of our four cases. It is well known that these drugs alone are relatively ineffective in the cure of bacterial endocarditis due to *Str. viridans*. Among the children treated with penicillin alone, the outcome has been excellent. Heparin was employed as an adjunct to the penicillin therapy of only one child. It does not seem to be necessary.

From this small group of fourteen children it is difficult to draw conclusions regarding prognosis or optimum therapeutic procedures. It is probable that many more children with subacute bacterial endocarditis have been treated with penicillin and it is hoped that the results will soon appear in the literature.

SUMMARY

The histories of four children with subacute bacterial endocarditis due to *Str. viridans*, who were treated with penicillin, have been reported in detail. The reports in the literature of ten other children treated in a similar manner have been reviewed.

Among this group of fourteen children only one died, and he had received inadequate dosage. A favorable outcome was achieved with total doses ranging from approximately 1.5 million to 11 million units of penicillin, administered in daily amounts of 80,000 to 300,000 units.

The route of administration seemed to make no difference in the outcome of this group of children, and no other drugs such as the sulfonamides or heparin seemed necessary.

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PENICILLIN IN THE TREATMENT OF THE SYPHILITIC INFANT

A Progress Report

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THIS report on penicillin treatment of the syphilitic infant supplements the observations previously recorded.[1, 2] In general, our enlarged experience confirms the initial impression that sodium penicillin given by intramuscular injection is a satisfactory treatment for the congenitally infected, syphilitic infant. This same experience has, however, caused us to modify our views concerning optimal treatment. This study is still in progress, and new interpretations and different emphases will arise as factual data accumulate. Nevertheless, a progress report seems desirable at this time.

We should like to point out that congenital syphilis is a severe and complex disease and should be considered apart from the acquired syphilis of the adult. It differs in its pathogenesis in that in congenital syphilis there is continual feeding of the spirochetes to the blood stream. The infection, involving all organs including bone, is more massive, intense, and serious because of interference in the rapid growth of tissues in the developing child. Other important differences are the immunologic immaturity of the fetus and the tendency to debility and secondary infection. The most acute stages of the disease are seen during the first few months of life, and it is especially during this phase that a higher mortality rate occurs because of the combination of intensity of infection by, and reaction to, the spirochetemia, and the concomitant debility and susceptibility to secondary infection. Treatment of infantile congenital syphilis is a far more complex problem than treatment of early syphilis in the adult, and requires the close cooperation of pediatrician and syphilologist.

MATERIAL

Thus far we have treated thirty-six congenitally syphilitic infants* with penicillin. Requirements for inclusion in this study are (a) a high or rising serologic titer for syphilis, and either (b) a clinically characteristic macular

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The results which are presented in this paper must be interpreted in the light of the fact that from June, 1943, the date of inception of the study, to the present, commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency in terms of units per milligrams has increased. The relative amounts of the several identified penicillin fractions G, F, X, and K, have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant, and that it may be significantly different today than it was originally. It is not now possible to assess the extent to which these changes may have affected the results here reported.

*The Philadelphia General Hospital supplied eighteen of these infants; the Children's Hospital, eleven; the Pennsylvania Hospital, two; the Hospital of the University of Pennsylvania, four; the Saint Luke's and Children's Medical Center, one.

eruption usually accompanied by dark-field positive, papular or bullous lesions, or (c) roentgenographic evidence of inflammatory reaction in the metaphyses of the long bones, with or without periostitis. Every infant meeting these criteria was treated as soon as the diagnosis was established. There was one exception, a premature infant who arrived from another hospital, dehydrated, acidotic, and moribund, and who succumbed in a few hours. No infant was treated on serologic evidence alone except where the titer showed increasing values. With such a group of patients, the high mortality characteristic of syphilis in the congenitally infected infant, which is most marked in the first 2 or 3 months of age, was anticipated.

The mean age of all of our infants at the beginning of treatment was 2 months. Five of these infants were one month old or less, twenty-two were between one and 3 months, six were between 3 and 8 months, and three between 8 and 30 months. Thirty-three were Negro and three were white. There were fifteen males and twenty-one females. Seventeen had skin lesions considered to be characteristically syphilitic; eight were dark-field positive. Thirty had unequivocal roentgen evidence of syphilis, ranging from generalized osteochondritis to widespread periostitis.

Five had no roentgen evidence of syphilis. One (Case 345), age 7 weeks, showed no roentgen evidence because the maternal infection was acquired very late in pregnancy and the baby's infection was in its incipiency as indicated by the rapidly mounting titer. Two (Case 328, 2½ years old and Case 368, 13½ months old) had passed the stage where early osseous lesions occur. The fourth (Case 148) was a very young infant 5 weeks of age, who had dark-field positive skin lesions and a high serologic titer but no evidence of osseous change. The father had secondary syphilis two months before the infant was born. The mother had a positive serologic reaction at the time of delivery. The fifth (Case 685) was a 13-week-old Negro infant, presumably infected very late in pregnancy. Two others (Case 392 and 63) had doubtful roentgen signs but unequivocal skin lesions and high serologic titers.

METHOD OF TREATMENT

The object of the study was to determine primarily what effect penicillin has in congenital syphilis, rather than to find the ideal dosage. A study of approximate dosage is now in progress, and obviously requires a larger series of cases.

Sodium penicillin was given intramuscularly every three hours over a period of seven days, then later over a period of fifteen days. At the outset, the individual doses were reduced for the first twelve or twenty-four hours, because of possible Herxheimer reaction. During the past year, however, no initial reduction in dosage has been used.

At first, we used the dosage approximately equivalent to 2,400,000 units for a 150 pound adult, or a total dosage of 16,000 units per pound of body weight. This dosage is similar to that employed in the study reported by Platou and his co-workers.[3] In the progress of our study it became obvious that this premise was untenable, and gradually this dosage was changed to 40,000, then 70,000

units per pound of body weight. Of the total cases, fifteen received dosages of sodium penicillin roughly in amount of 20,000 units or less per pound of body weight. Twenty-one received higher dosages while thirty-one received single courses. The plan of study was to have a monthly follow-up visit for complete physical examination by the pediatrician, blood drawn for serologic study, and repetition of the roentgenograms until they became normal. After the serologic reaction remained negative for six months, follow-up visits were planned at slightly longer intervals. Examination of cerebrospinal fluid, while not routinely done at the beginning of the study, is now being done at the onset and periodically after. No other antisyphilitic therapy was given. Supporting treatment in the form of fluids, transfusions and, electrolytes was an important consideration, especially in the younger and debilitated patients.

RESULTS OF TREATMENT

Clinical and Serologic Results.—Clinical and serologic results are tabulated in Table I. In thirty-two of the thirty-six infants, the initial clinical response was uniformly good. Cutaneous and mucosal lesions healed rapidly and no positive dark-field examinations were found after twenty-four hours. Appetite, nutrition, and general activity improved. In those instances where clinical improvement was not manifest, the underlying difficulty was marked anemia, debility, or feeding difficulty associated with anorexia and vomiting or with marked nasal crusting and discharge from the nose.

The average time for the blood reagin titer to become negative was 260 days in those cases treated with less than 20,000 units per pound, whereas it was 154 days when the dosage was more than 20,000 units per pound of body weight. For statistical comparison of the two groups, the three older infants (Cases 88,

TABLE I. SEROLOGIC STATUS AT SPECIFIED TIMES

FOLLOW-UP AFTER START OF THERAPY	TOTAL CASES OBSERVED	CLINICALLY WELL				DEAD
		SERO-NEGATIVE	DECLINING	UNCHANGED	RE-TREATED	
Over 20,000 Units per Pound Body Weight						
60 days	12	0	4	5		3
120 days	8	2	4			
180 days	8	3	3*		1	
270 days	7	3	2			
365 days	6	5	0			
480 days	4	4				
599 days	1	1				
730 days	1	1				
Total	12					
Under 20,000 Units per Pound Body Weight						
60 days	21	2	5	5		3
120 days	16	5	5	4	1	1
180 days	11	6	1			
270 days	10	1				
365 days	8	8				
480 days	5	4				
599 days	2	2				
730 days	1	1				
Total	21					

*Case 58.—Clinical relapse (dark-field positive skin lesions). Re-treated.

368, and 328; 23, 13½, and 30 months of age, respectively) were omitted. Thus the two groups were comparable as to mean age (2 months). Statistical comparison between the response of the two groups to treatment showed no significant difference. Clinically, however, it was our very definite impression that those infants treated with the higher dosages and especially the higher initial doses did better on the whole. This point, however, will need further observation on a greater number of cases. The serologic response is slower than that

1A. *1B.*

Fig. 1*A*.—W. H., Feb. 12, 1945. Age, 4 weeks. Children's Hospital of Philadelphia. Feeding problem. Positive serologic reaction for syphilis. Long bones reported as negative, left femur shows slight rarefaction at outer distal end of metaphysis which became more manifest on March 5.

Fig. 1*B*.—W. H., March 9, 1945, at outset of treatment. Kline test 128 units of reagin. Age, 8 weeks, weight, 8 pounds, 6 ounces. There is destruction of the metaphysis of the left femur with obliteration of the normal architecture and a mushroom-shaped deformity. In the upper ends of the tibia and fibula the destructive process involves more of the medulla. Periosteal proliferation along the shaft is evident.

obtained in adults. This supports the statement that congenital syphilis cannot be considered to be a proportionately diminutive example of adult syphilis.

Relapses.—One infant (Case 58), whose treatment began at 3 months and amounted to 18,000 units per pound in an eleven-day period, showed marked clinical improvement and a steadily declining serologic titer on three follow-up

visits, yet at 177 days was found to have typical macular skin lesions which were dark-field positive. Re-treatment, using 67,000 units per pound in an eight-day period brought prompt clinical and gradual serologic improvement resulting in seronegativity 168 days later, which condition has remained for the year following.

This was the only clinical relapse. There was no instance of serologic relapse that was sustained. However, two infants (Cases 89 and 323) each showed one reversion to seropositivity before becoming consistently seronegative. Another infant (Case 328) became seronegative after re-treatment, then weakly seropositive just before it was lost to follow-up.

Fig. 1C.—W. H., March 20, 1945, eleven days after beginning treatment, using 5,000 units of penicillin every three hours, total, 560,000 units in fourteen days. Legs were swollen and painful on motion. The calcification is obviously being rapidly deposited in an area more extensively involved than was appreciated from preceding films. This rapid change has not previously been noted in the natural history of the congenitally infected syphilitic infant.

Osseous Changes.—Osseous changes as revealed in serial roentgenograms showed characteristic involution. There were three instances, however, where dactylitis, either mild or moderate, showed clinical and roentgen progression before regression. In two younger infants with marked osteochondritis (Cases 398 and 802, aged one and 1¾ months respectively) the inflammatory process in and around the metaphysis became more easily demonstrable in the roentgenogram because of calcification. This, in all probability, is a part of the healing process.

Re-treatment.—Five cases were re-treated for various reasons. Four were in the low dosage group and occurred early in the study. The older infants were also in the low dosage group.

CASE 88.—A 23-month-old Negro female infant weighing 18 pounds had osseous and serologic evidence of syphilis, a marked "saddle nose," and malocclusion due to a short central maxilla. There was atrophy of the lower limb musculature, inability to walk, or even to stand. The knee and ankle jerks were exaggerated. Over a period of eleven days 16,000 units of penicillin were given without reaction. Improvement both roentgenographically and clinically followed. At 127 days after onset of treatment she was beginning to walk but still had slightly abnormal reflexes. Because the high serologic titer remained unchanged, she was re-treated at 356 days by administering 31,900 units per pound in eighteen days. The clinical improvement continued while the serologic response was less prompt. When last seen at 678 days, the serologic titer was still two Kline units. Cerebrospinal fluid was at no time abnormal.

CASE 328.—A 30-month-old Negro girl had a mild degree of congenital syphilis as indicated by a Kline titer of 64, generalized lymphadenopathy, and splenomegaly. She received 18,750 units per pound of body weight in seven days. The serologic titer remained between 64 and 128 Kline units, so re-treatment was begun at 215 days with 67,400 units per pound in a fifteen-day period. At 331 days the infant was seronegative for the first time, but at 371 days showed 32 Kline units of serum reagin. The case was thereafter lost to follow-up.

CASE 199.—An 8-month-old female weighing 15 pounds, 1½ ounces, had serologic and roentgen evidence of syphilis. The outstanding physical finding was hydrocephalus. The head was so large that she was unable to lift it or sit alone. Aside from nystagmus the neurologic examination was negative. Over a period of seventeen days, 16,060 units per pound of body weight were given without reaction. During the month following onset of penicillin therapy there was a marked regression in hydrocephalus, the head circumference receding from 22 inches to 19 inches with overriding of the bony plates (normal circumference 17 to 18 inches). The chest circumference remained the same. The child became more alert, more active, and gained weight, yet the serologic titer remained stationary. The osseous lesions showed marked improvement by roentgenogram. Because of the low initial dosage, and in hopes of accelerating the serologic response and clinical improvement, she was re-treated at sixty-five days, using 19,120 units per pound over a five-day period. At 186 days after the initial therapy (age 14 months) she was sitting alone, and at 256 days became seronegative and remained so throughout the observation period lasting 536 days. The spinal fluid had never shown any abnormality. At the time of last examination she seemed normal in every way.

CASE 58.—A 3-month-old Negro male infant with marked initial clinical infection, a blood serologic titer of 128 Kline units, and roentgen evidence of involvement of the long bones, received 18,500 units per pound of body weight over a nine-day period. The clinical response was prompt and serial serologic tests showed a declining titer, yet at follow-up when 177 days old he showed scattered macular skin lesions which were dark-field positive. He was re-treated with 67,600 units per pound of body weight over an eight-day period with no untoward reaction. His serologic titers were slightly higher for the next three months but he became seronegative on the three hundred and forty-fifth day, and had remained so when last observed on the six hundred and fifty-third day. There was no history to suggest a re-infection.

CASE 398.—A one-month-old Negro female infant weighed 5 pounds, 3 ounces at birth and 5 pounds, 5 ounces when admitted. She was in a severe state of debility, showed signs of pneumonia and generalized desquamation of the skin. There were roentgenographic signs of periosteal involvement of all long bones, and considerable osteochondritis. The Kline titer was 128 units. During the eight-day course of treatment when she received 22,600

units per pound of body weight, there was rapid calcification in the previously existing inflammatory process in the bone. Transfusions of blood and plasma were required, and improvement was slow. At the age of 2 months she still weighed only 6 pounds, one-fourth ounce and had extensive bone changes and a Kline titer of 256. At the age of 3 months, when the Kline titer was still unchanged and the infant was still in a poor nutritional state weighing 7½ pounds, it was decided to re-treat, because at that time the dosages appeared to be far too low. She received 40,000 units per pound over a sixteen-day period beginning sixty days after her first course of therapy. Clinical improvement was prompt and marked. Within a month she gained almost 4 pounds. At 155 days she was seronegative and remained so throughout her 372-day observation period.

Fatalities.—Since the two fatal cases mentioned in our previous report we have had five additional deaths, making a total of seven or 19.4 per cent.

CASE 47.—A Negro, female, premature infant weighing 3 pounds, 14½ ounces at birth, was the first child of an untreated seropositive mother. The infant had "snuffles," enlargement of the liver and spleen, periostitis of the bones roentgenographically demonstrated in the right arm and leg, and serologic reaction of 64 Kline units. She also had signs suggesting a congenital cardiac defect, probably patent ductus arteriosus. A seven-day period of treatment was given, with 18,000 units per pound of body weight. Half doses were given for the first twenty-four hours. There was a rise of temperature to 100.5° F. twelve hours after treatment started, but the baby showed no other untoward signs. One week after completion of therapy, notwithstanding general clinical improvement, the infant developed diarrhea, and despite active treatment died four days later on the seventeenth day after onset of penicillin therapy, when 35 days old. There had been a case of diarrhea in the same nursery three weeks previously, at which time all contacts received 0.5 c.c. immune human serum globulin.* Post-mortem blood culture showed hemolytic *Staphylococcus aureus.* No autopsy could be obtained.

CASE 112.—A 6-week-old Negro female infant weighing 8 pounds, 3 ounces, had "snuffles," generalized adenopathy, enlargement of liver and spleen, enlargement of the epiphyses at the wrists, and partial paralysis of the left arm. There were extensive osseous changes. On admission the temperature was 102° F. and ranged from 100 to 104° F. for the first three days. The hemoglobin was 53 per cent. Penicillin therapy was begun the third day after admission. Thereafter, the temperature was normal but anorexia persisted and diarrhea manifested itself intermittently. Only one-half of the calculated penicillin dosage of 70,000 units per pound was given, as the course was steadily downhill and the infant expired on the ninth day of treatment. The first three doses were only one-tenth the subsequent doses. Fever of 101° F., present for the first two days after admission, persisted for another twenty-four hours after treatment started, then fell to normal and remained there. The infant showed no immediate reaction to treatment. Autopsy showed generalized osteochondritis, hyperplasia of spleen, and aspirated debris resembling milk curds in the bronchial tree.

CASE 286.—An emaciated, ill, dehydrated, 5-week-old, Negro female infant weighed 5 pounds, 10 ounces (birth weight 5 pounds, 11 ounces) when transferred from another hospital where she had been treated for bronchopneumonia. She was delivered at eight months of a mother with untreated syphilis. Previous roentgenograms showed extensive osseous involvement. The Kline titer was 128 units. The infant showed respiratory distress but no signs of pneumonia. The hemoglobin was 29 per cent, leucocytes 28,200. Penicillin was begun using 350 units every three hours, and the child gradually became weaker and died after the fifth injection. Autopsy revealed diffuse bronchopneumonia and there was also moderate periportal fibrosis in the liver and diffuse hyperplasia of the spleen.

CASE 397.—A 3-month-old, Negro male infant, born at term of an inadequately treated syphilitic mother, weighed 7 pounds, 4 ounces at birth. The admission weight was 8 pounds,

*This was being used experimentally in a study of its protective value in epidemic diarrhea of the newborn. No positive evidence of value was obtained.

6 ounces. He had seemed well until twenty-four hours before admission to another hospital, when he developed fever, cough, and purulent nasal discharge. The infant was emaciated, had physical signs of pneumonia, macular lesions on the skin, extensive characteristic changes on the roentgenograms of the long bones, and strongly positive Kolmer and Kahn reactions. The temperature on admission was 105° F. After two days of sulfadiazine the chest signs cleared and penicillin was given over a period of ten days, 26,000 units per pound of body weight. The first ten doses were reduced to 253 units each. The baby improved somewhat at first but on about the tenth day of therapy began to vomit, became listless, and had intermittently loose stools. Penicillin was discontinued. Despite parenteral fluids, plasma, blood transfusions, and careful dietetic management, his distention and diarrhea continued. He developed an otitis media. The course was downhill and he died twenty-seven days after the onset of penicillin treatment. Roentgenograms taken post-mortem showed some healing of the extensive osteochondritis. Permission for autopsy was not granted.

CASE 507.—A one-month-old Negro female infant weighed 5 pounds, 2 ounces at birth. The mother was incompletely treated for syphilis during pregnancy. On admission, the infant weighed 5 pounds, was in poor condition, and showed marked roentgen and serologic evidence of syphilis. The initial doses of penicillin were 500 units every three hours for the first thirty-nine hours, 1,000 units every third hour for the next three doses, and thereafter, 2,000 units at each dose. There was no immediate reaction. Transfusions of blood and plasma and parenteral fluids were given for the first few days until improvement was manifest. The total dosage averaged 36,300 units per pound of body weight and was completed in a period of thirteen days when the patient was discharged in good condition. Later it was learned that she died thirty days after onset of penicillin treatment, having been brought into the receiving ward of another hospital in a moribund state. Malnutrition was the ascribed cause of death. There was no autopsy. This was an illegitimate and unwanted child and family cooperation had always been poor.

CASE 552.—An 11-week-old, debilitated, Negro female infant was admitted weighing 7 pounds, 8 ounces. She had extensive desquamation and macular skin lesions, "snuffles," paresis of the left arm, marked periostitis and osteitis by roentgenogram, and a serologic titer of 256 Kline units. The hemoglobin was 45 per cent. Penicillin was begun, using a total dosage of 37,300 units per pound of body weight. There was no initial reduction, each dose being 5,000 units, given every three hours. No immediate reaction occurred. Two blood transfusions were given so that during the first three days of treatment the hemoglobin rose to 72 per cent. There was marked clinical improvement. Then the "snuffles" became more marked, the infant took feedings poorly, vomited occasionally, and had intermittent loose stools. The infant failed progressively and died on the seventh day of treatment, having received one-half the calculated dosage. Spinal fluid collected immediately post mortem showed the protein to be 75 mg. per 100 c.c., and tests for syphilis by the Wassermann and mastic technique were strongly positive. Post-mortem blood samples showed a blood urea nitrogen of 65 mg. per 100 c.c. Autopsy showed injected mucosa of the terminal ileum and colon, generalized inflammatory changes in the mesenteric lymph nodes, and some aspirated debris in the bronchial tree with partial atelectasis. There was also marked proliferation at the epiphyses of the wrists, the only long bones examined.

CASE 299.—A well-nourished, 6-week-old, Negro male infant weighed 9 pounds, 7 ounces. His mother was unmarried, had contracted syphilis late in pregnancy, and had received no treatment. There was a two-week history of "snuffles" and eruption on the palms and soles, which proved to be dark-field positive. Hemoglobin was 47 per cent and rose to 57 per cent after two transfusions. Penicillin was administered over a period of twelve days, the dosage being 61,540 units per pound of body weight. The immediate response and general clinical course were good, with the exception of development of clinical evidence of extensive dactylitis. Roentgenograms showing marked periosteal changes on the sixth day of therapy, at which time there was also microscopic hematuria, some albuminuria, and a few casts, while the blood showed 5.4 Gm. of protein and 10 mg. urea nitrogen per 100 c.c.

The dactylitis gradually receded. Roentgenograms which were negative on admission showed the appearance of the inflammatory changes of periositis and osteochondritis, in the long bones and metacarpals followed by gradual healing. The infant left the hospital twenty-eight days after the onset of therapy in good general condition, the only abnormality being slight but firm swelling of the fingers. He was seen at frequent intervals during which time his improvement continued and his serologic reagin titer declined steadily. He was brought in with a mild respiratory infection, temperature 100.6° F., history of nasal discharge for two days, and anorexia for one day. There were some rhonchi in the chest but since the infant seemed only mildly ill, he was given the usual directions for fluids, nose drops, feedings, and sulfadiazine, 0.13 Gm. every four hours. Later it was learned that he became much worse and died at home two days after he had been seen at the hospital. There was no autopsy.

During the course of this study it was noted that occasional infants with congenital syphilis showed signs of toxemia as manifested by anorexia, diminishing activity, and occasionally diarrhea. This has also been noted in arsenotherapy. Whether or not it is a Herxheimer reaction alone or whether it should be considered inherent to the disease cannot be stated. With our increasing experience the latter seems more likely. However, attention is called to the fact that it does occur, and, as such, may offer a serious complication of which one should constantly be aware in order to anticipate and offset further complications. It is to be pointed out that when intercurrent infection is present (e.g., from staphylococcus or pneumococcus) the dosage of penicillin normally used for syphilis is insufficient to care for these complications. This is especially the case if the initial dose of penicillin is reduced in infants to prevent the so-called Herxheimer reactions. It is noteworthy that this study was begun anticipating such reactions, but since even the occasional rise of temperature occurring within the first few hours did not prove harmful, the small initial dosage was abandoned and the tendency has been to increase the total dosage and lengthen the treatment period.

It is our feeling that in some infants the lower initial dosage may be more harmful to the infant than the higher initial dosage, in that any secondary infection which may be present is not cared for, even though the syphilis may be favorably influenced. The older antisyphilitic remedies (e.g., neoarsphenamine, Mapharsen and bismuth) had little direct effect on intercurrent infection. For the first time with penicillin we have a drug equally effective against syphilis, pneumonia, and other forms of localized pyogenic infection and septicemia. In determining the dosage to be used, the total picture of infection of the infant should be considered, and the dosage regulated accordingly. Less satisfactory results are obtained by considering penicillin therapy for syphilis only.

Our fatal cases illustrate the necessity of active supportive treatment during the penicillin therapy period. One of the recent patients (Case 763) was an emaciated, dehydrated infant weighing 5 pounds, 3¾ ounces, who responded well for the first two weeks, but after completion of penicillin therapy became much worse clinically. "Snuffles" and nasal crusting made breathing and feeding difficult. She was listless and had occasional diarrhea. It was only vigilant pediatric nursing that prevented her demise. The need for special nursing care of the debilitated syphilitic infant cannot be overemphasized.

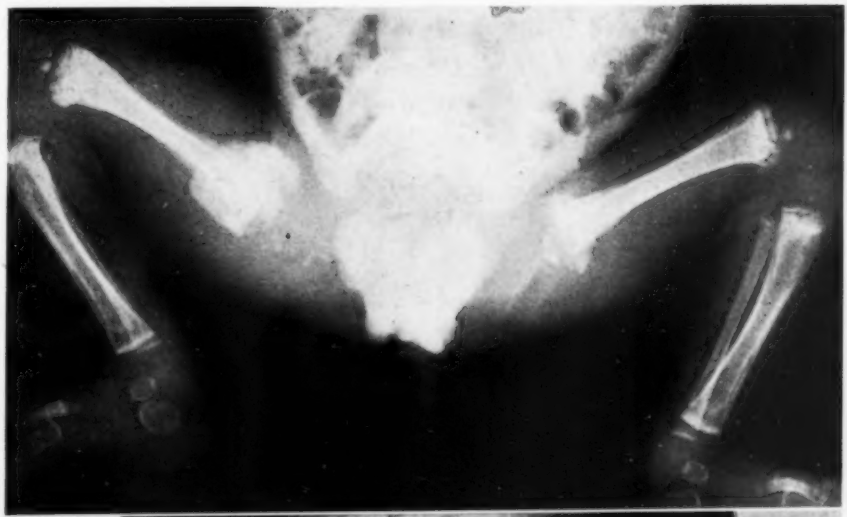
Had penicillin therapy been withheld until each patient was put in optimal condition by the addition of blood, plasma, electrolytes and fluids, more infants would have died *before* penicillin treatment and consequently would not have been included in this study. Under such conditions the number of fatalities would have been lower.

FIG. 2A.—J. S., March 22, 1946. Lower extremities. Age, 6 weeks. Philadelphia General Hospital. Strongly positive serologic test for syphilis. Thighs seemed normal in size and motility, zone of rarefaction evident beneath ends of metaphyses with fragmentation of the metaphyseal-epiphyseal line, and in some instances a mushroom-shaped deformity thought to be due to multiple infractions.

Four of the five deaths occurring during treatment were during the earlier months of this study. It is our feeling that death was not directly related to the penicillin, but rather to the combination of the underlying poor condition of the syphilitic infant and intercurrent infection. Better pediatric management is essential in reducing such mortality. In the two infants who died outside the hospital, it would seem that one death (Case 299) was due to an overwhelming respiratory infection and the other (Case 507) due to the malnutrition of maternal neglect with perhaps an unrecognized concurrent infection. Neither was related to penicillin or to the congenital syphilis directly.

The infrequency of relapse is noteworthy. It raised the question of a different immunologic relationship between the infected mother and the fetus.

2B.



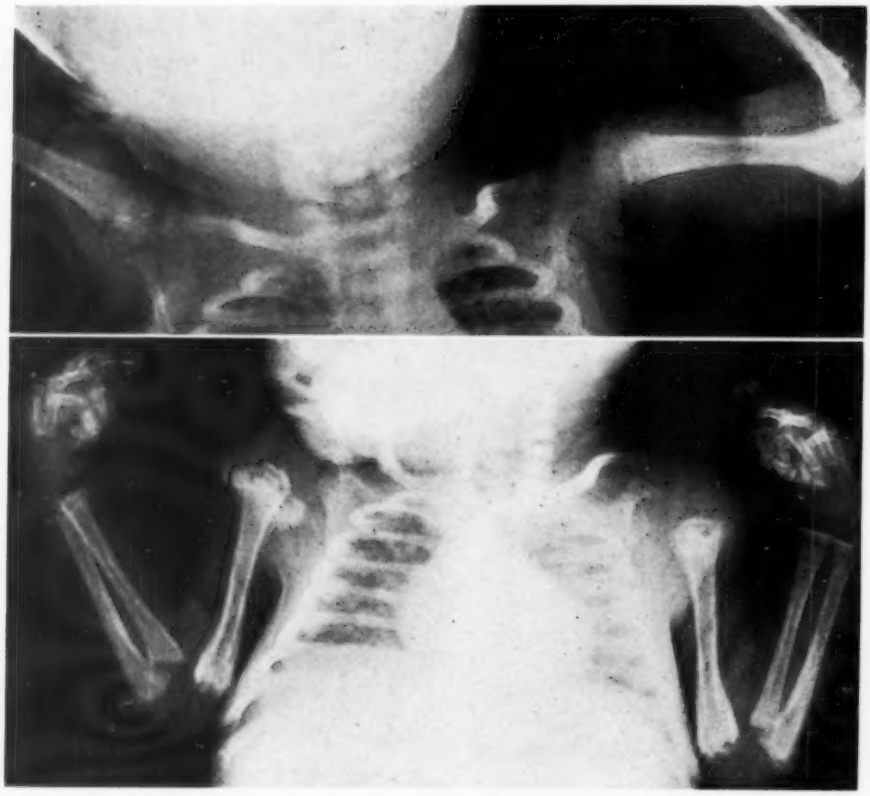
2C.

Fig. 2B.—J. S., April 10, 1946. Lower extremities. Three days after completion of treatment (1.04 million units of penicillin from March 25, 1946 to April 7, 1946), the thighs became markedly swollen and painful. Patient assumed a constant frog-like position. Roentgenogram shows rapid, unexpected appearance of excessive calcification in soft tissues in proximal portion of right femur.

Fig. 2C.—J. S., April 26, 1946. Lower extremities, nineteen days after completion of treatment. More periosteal proliferation and less of the denser, more massive lesions at the proximal ends of the femora are seen.

In acquired syphilis of the adult treated with penicillin, the cumulative failure rate caused by relapse or reinfection reaches 15 per cent after eleven months.[4] It is of interest to note that in our admittedly small number of cases of congenital syphilis, no relapse was observed within one year after adequate treat-

2D.



2E.

Fig. 2D.—J. S., March 22, 1946. Upper extremities, before treatment.

Fig. 2E.—J. S., April 10, 1946. Upper extremities, three days after completion of treatment. Increased calcification at proximal end of right humerus and generalized periosteal proliferation are evident.

ment. This difference between acquired and congenital syphilis under penicillin treatment seems to indicate two possibilities: (1) the high cumulative failure rate in acquired syphilis is due more to reinfection than to relapse, and (2) congenital syphilis after treatment with penicillin produces more permanent immunologic resistance than acquired syphilis under similar conditions. More prolonged and better controlled observations on a larger series of cases of congenital and acquired syphilis will give us the final choice between these two important possibilities, both from a theoretical and a practical point of view.

A special point of interest is the intensity and rapidity of osseous changes following administration of penicillin in some of our cases (Cases 802, 398, 299, and 763).

More rapidly progressive destructive and proliferative lesions may become evident in the long bones of infants with congenital syphilis under the influence of penicillin. They are very reminiscent of similar pictures observed in acute pyogenic osteomyelitis, although in their pathogenesis and etiology they are different. In both instances, the pathologic reaction is primarily due in the first place to rapid destruction of spirochetes or staphylococci with elimination of necrotic debris, and to periosteal and soft tissue inflammatory reaction which is then closely followed by osseous repair.

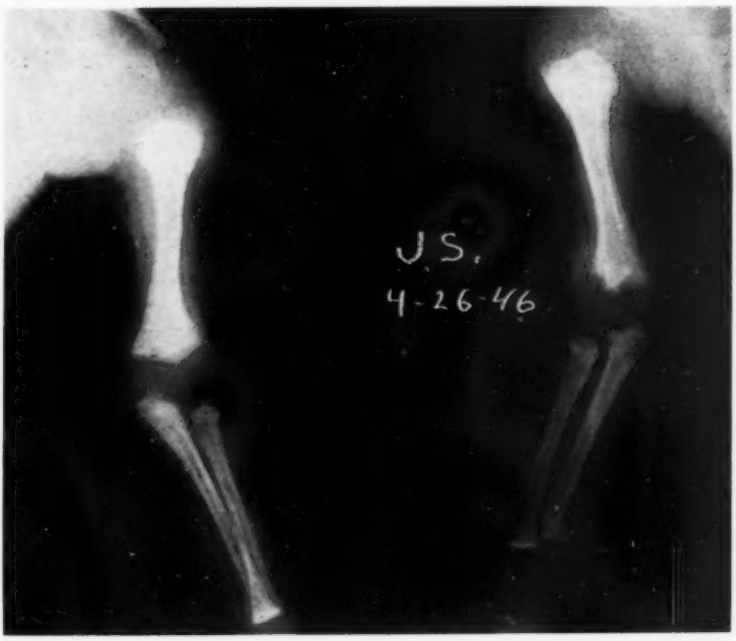


Fig. 2*F*.—J. S., April 26, 1946. Upper extremities, nineteen days after treatment finished. Previous extensive calcification has disappeared, periosteal changes still evident.

In analogy to the roentgen findings in acute pyogenic osteomyelitis,[5] calcification may become apparent in congenital syphilis following treatment with penicillin, through very extensive osteoblastic activity of the periosteal layer around the metaphyses of the long bones, especially of the femur or humerus. Such calcification, bearing some resemblance also to calcified subperiosteal hemorrhages in scurvy, appears very early after treatment and leads to very marked temporary deformity of the bones (Fig. 1). At first the calcification may be very irregular and may give the false impression that it involves also the surrounding soft tissue. Repair is rapid and progressive. (Fig. 2.)

DATA ON THIRTY-SIX INFANTS WITH CONGENITAL SYPHILIS TREATED WITH PENICILLIN*

CASE	AGE IN MO.	CLINICAL EXAM. SKIN	CLINICAL EXAM. DARK FIELD	CLINICAL EXAM. BONE X-RAY	S.T.S. IN KLINE UNITS	NUTRITION STATUS	WT. IN LB. AND OZ.	PENICILLIN UNITS PER POUND	PENICILLIN—INTRAMUSCULAR ALIQUOT DOSES EVERY 3 HR. TOTAL DOSE	IN DAYS	REDUCED INITIAL DOSE	REACTION	CLINICAL RESPONSE	DAYS POST-PEN. FIRST SUSTAINED NEG. S.T.S.	NO. DAYS FOLLOWED	COMMENT
Total Dosage—Less Than 20,000 Units of Penicillin per Pound Body Weight																
43	1½	+	+	+	64	Poor	6— 3	16,129	100,000	9	√		Good	100	297	
47	⅔	0		+	128	Poor	4— 7½	18,099	80,000	7	√				17	Premature; probable congenital cardiac defect; general debility; slight improvement, then diarrhea; died at age 35 days; no autopsy
58	3	0		+	128	Poor	12—11	18,373	236,000	11	√	Rash	Good	345	653	Relapse; developed dark-field positive lesions while bones and S.T.S. improving; re-treated at 177 days; 1,200,000 units in 8 days
63	4	0		±	Pos. Not Quantitative	Poor	12—14	18,615	242,000	9	√		?		207	Gradual decline in S.T.S. titer to 4 units; lost to follow-up
88	23	0		+	32	Fair	18	16,000	288,000	11	√		Good		678	Re-treated after 386 days; seroresistance 930,000 units in 18 days—S.T.S. ± but marked clinical improvement
89	4	0		+	64	Poor	7—11	18,440	142,000	10	√		Good	199	608	
112	1½	0		+	128	Poor	7—11	10,631	111,625	8	√				8	Died during treatment; acute nutritional disturbance; autopsy, bronchopneumonia
113	1¾	0		+	128	Fair	9	11,111	100,000	7	√		Good	217	459	
155	2	+		+	128	Good	11—11	16,410	192,000	6	√	Temp. 101-102° F. 5th day	Good	96	461	

*Total dose computed on basis of weight, administered intramuscularly every third hour in aliquot doses, except where indicated smaller initial doses were employed.

initial doses were employed.

199	8	0		+	64	Fair	15— 1½	16,060	240,950	17	√		Good	256	536	Re-treated after 65 days, 350,000 units, to facilitate already improving hydrocephalus
207	3	+	+	+	128	Poor	8	16,094	128,750	15	√		Good	287	483	
286	1¼	0		+	32	Poor	5—10	310	1,750	2	√				2	Died during treatment; debility, anemia; autopsy, bronchopneumonia, hepatitis
328	30	0		-	64	Fair	24	18,750	450,000	7			Good		371	Re-treated after 215 days, 1,800,000 units in 15 days, for S.T.S. improvement; Kline, 32 units at 371 days
343	3	+		+	128	Good	9—13	17,755	174,000	8			Good	165	165	Lost to follow-up
368	13½	+		-	64	Good	24	14,581	399,960	8			Good ?		59	Lost to follow-up; Kline, 64 units at 59 days
Total Dosage—More Than 20,000 Units of Penicillin per Pound Body Weight																
87	1½	+		+	128	Poor	3	26,667	91,000	14	√		Good	224	576	Marked debility; good response
148	1¼	+	+	-	128	Poor	6— 8	22,246	144,600	15	√		Good	247	626	
285	1¼	+	+	+	128	Fair	8— 2	74,000	301,200	15	√		Good	156	358	
293	4	+		+	64	Good	11— 8	52,087	600,000	7	√	Temp. 102° F. 2nd dose; edema; hematuria	Good	363	363	S.T.S. doubtful at 196 days; no follow-up until 363 days
299	1½	+	+	+	32	Good	9—12½	61,540	600,000	12	√	Dactylitis 6th day	Good		93	Excellent clinical response; later died at home; no autopsy
323	3	0		+	128	Poor	9— 1½	26,373	240,000	13	√		Good	180	298	S.T.S. negative at 111 and 139 days; 32 units at 160 days
344	½	+		+	32	Good	7— 7	21,570	159,600	7			Good	69	441	
345	2	+		-	128	Good	7— 8½	20,000	150,000	7		Temp. 104° F. Rash	Good	47	474	
397	3	+		+	Pos. Not Quantitative	Poor	8— 6	24,837	202,400	10	√				27	Died; bronchopneumonia; septicemia, otitis; no autopsy
392	1	+		±	128	Fair	6	20,000	120,000	8		Temp. 101° F.	Good		81	S.T.S.; Kline, 16 units when lost to follow-up

DATA ON THIRTY-SIX INFANTS WITH CONGENITAL SYPHILIS TREATED WITH PENICILLIN—CONT'D

CASE	AGE IN MO.	CLINICAL EXAM.			S.T.S. IN KLINE UNITS	NUTRITION STATUS	WT. IN LB. AND OZ.	PENICILLIN UNITS PER POUND	PENICILLIN—INTRAMUSCULAR ALIQUOT DOSES EVERY 3 HR.				CLINICAL RESPONSE	DAYS POST-PEN. FIRST SUSTAINED NEG. S.T.S.	NO. DAYS FOLLOWED	COMMENT
		SKIN	DARK FIELD	BONE X-RAY					TOTAL DOSE	IN DAYS	REDUCED INITIAL DOSE	REACTION				
398	1	0		+	128	Poor	5— 5	22,641	120,000	8		Shock, 4 hr.	Good	155	372	Re-treated after 60 days to accelerate improvement
507	1	0		+	128	Poor	5	36,320	181,600	13	√		Good		30	Good initial response; later, died at home; no autopsy
508	8	0		+	Pos. Not Quantitative	Fair	19—12	38,071	750,000	16			Good	106	279	
513	2	+	+	+	128	Poor	7— 9	35,789	272,000	15	√	Rash	Good	108	262	
517	2½	+	+	+	256	Poor	7—14	36,252	286,400	19	√	Temp. 102° F. after 2nd	Good		74	
552	2½	+		+	256	Poor	7— 7	37,333	280,000	7	√				7	Died during treatment; acute nutritional disturbance; autopsy
685	3¼	0		-	128	Fair	11— 1½	69,084	759,924	15			Good	31	129	
756	2	0		+	256	Fair	10—11	66,977	720,000	16			Good		63	
758	1¾	0		±	256	Fair	10— 3	70,244	720,000	16		Temp. 102° F. after 8 hr.	Good		39	
763	1¾	0		+	512	Poor	5— 1	74,913	393,294	16			Slow		60	Stormy course; marked debility; final improvement before discharge
802	1¾	0		+	128	Poor	8— 6	65,882	560,000	15		Temp. 101° F. after 3rd dose	Good		15	

REACTIONS

The reactions observed and associated with treatment were predominantly of three types, fever, skin eruptions, and those associated with accelerated osseous involution. (Table II.) Febrile reactions occurred in seven of the thirty-six infants and were usually seen within the first six to eight hours. They were of short duration and in only one infant (Case 293) associated with systemic signs. This infant showed generalized edema, hematuria, and a temperature of 102° F. six hours after onset of therapy. The temperature returned to normal in several hours. The other signs disappeared the next day.

TABLE II. REACTIONS TO PENICILLIN THERAPY

CASE	AGE (MONTHS)	UNITS OF PENICILLIN	TIME OF REACTION	TYPE OF REACTION
398	1	4,000	4 hours	Shock; temperature 94° F.
345	2	5,000	4 hours	Temperature 104° F.; rash
293	4	3,000	6 hours	Temperature 102° F.; edema; hematuria
517	2½	1,000	6 hours	Temperature 102° F.
758	1¾	18,000	7 hours	Temperature 102° F.
802	1¾	15,000	8 hours	Temperature 101° F.
392	1	12,000	15 hours	Temperature 101° F.
58*	10½	175,000	30 hours	Rash
513	2½	19,500	60 hours	Rash
155	2	114,900	5 days	Temperature 102° F.
299	1½	256,000	6 days	Dactylitis

*Re-treatment.

The skin eruptions were of a maculopapular nature, appeared between six and sixty hours in the three patients where noted, and were transient. They were most probably accentuations of syphilitic lesions induced by therapy (cutaneous Herxheimer).

One infant (Case 398) became hypothermic, limp, and was in a state of mild circulatory collapse within four hours after the first dose of penicillin.

One infant (Case 249) showed marked dactylitis on the seventh day after treatment commenced.

Two other infants (Cases 756 and 758) showed exacerbation in the dactylitis already present at onset of therapy.

The four infants in which the usual initial clinical improvement was not manifest were already in very poor condition, yet showed no untoward reactions which could be related directly to therapy.

In no case was there any direct relationship between age of patient, amount of penicillin, and time of reaction. More recent experience has proved that the so-called Herxheimer reaction is not to be feared and that in the debilitated infants, as mentioned before, it is even more desirable to give larger initial dosages to offset possible secondary infection.

Occasionally diarrhea was encountered during therapy, but in about the same incidence as in other nonsyphilitic patients receiving no penicillin.

SUMMARY

Thirty-six infants with congenital syphilis were treated with intramuscular penicillin in dosages ranging from 11,000 to 75,000 units per pound of body weight over periods of seven to fifteen days.

Fifteen received total dosages of less than 20,000 units per pound of body weight, twenty-one received over 20,000 units per pound of body weight. When three older infants were removed from the lower dosage group, and the two groups were statistically comparable, there was no significant difference in results. The only case of clinical relapse, however, and three other cases meriting re-treatment, occurred in the low dosage group. The impression was that clinical improvement occurred more rapidly with the higher dosages.

Nineteen have become clinically well and seronegative.

Six became clinically well, but remained seropositive. Three were seropositive when lost to follow-up at 74, 59, and 81 days after beginning treatment, and two were clinically well but serologically doubtful. Four of these six patients were in the lower dosage group.

Seven died, five while hospitalized for penicillin therapy, two much later after initial clinical improvement.

Four have been treated too recently to evaluate beyond the prompt clinical improvement.

There was no case of serologic relapse in the whole group, and only one clinical relapse, which was in the group receiving the lower dosage.

CONCLUSIONS

From observations during this study the following conclusions seem tenable:

1. The recommended total dosage of sodium penicillin is not less than 75,000 units per pound of body weight, given intramuscularly every three hours in aliquot doses, and the treatment course should not be less than fifteen days.

2. There is no need for an initial low dosage, even in debilitated infants. Higher dosages seem helpful in combating secondary infection.

3. There are cases manifesting symptoms referable to toxemia (anorexia, weakness, vomiting, occasionally diarrhea) where serious complications can be avoided only by anticipation, early hospitalization, and prompt and vigilant pediatric supervision.

4. Syphilis is a different and more serious infection in the congenitally infected infant than in the early acquired infection of the older person, and as such it is a problem requiring the closest cooperation between the pediatrician and the syphilologist.

5. The optimum time dosage relationship is still to be worked out.

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METHEMOGLOBINEMIA

Two Cases in Newborn Infants Caused by Nitrates in Well Water

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CASE HISTORIES

Case 1.—V. C. G. was a girl 5 weeks old. Her family and prenatal history were not contributory. She was fed with a powdered milk formula.

On April 3, 1945, the family doctor gave her a prescription for a mild cough.

On April 4, she did not enjoy her feedings and looked a little unwell.

On the morning of April 5, the mother found the infant rather cyanosed. During the same day she drank very poorly and had about ten yellow stools, which became progressively more liquid. The condition grew worse from hour to hour, and the child was hurried to the clinic in the evening.

Physical Examination.—Good nutrition. Slate-colored cyanosis of the whole body, more marked on face and hands, more evident when the child cried. No icterus. On the whole, the infant presented the appearance of complete apathy. The respiratory rate was 90 per minute; the pulse, 200. Rectal temperature was 36.2° C. (97.2° F.). There was no movement of the nostrils with respiration, and no dehydration. The spleen and the liver were not felt. The lungs and the throat were normal. The heartbeat was regular and accelerated. Its volume was normal. The heart sounds were of good quality. No murmurs were heard.

Inasmuch as a diagnosis of sepsis was entertained, blood was drawn for culture. This blood was of normal fluidity, but its color was frankly chocolate brown. It was not hemolized. It contained large amounts of methemoglobin, but no quantitative study was made. From the color of the blood[1] it was thought that the methemoglobin constituted about 50 per cent of the total pigment. We decided to transfuse the patient. In the course of preparation for transfusion, the condition became really alarming. When we cut the skin to denude the vein, the child did not cry. She received 30 c.c. of citrated blood. After a few minutes her condition was much better; her respiration was less irregular, her pulse less rapid, and the cyanosis less marked. The improvement was more obvious on the next day. The color of the skin was almost normal. There was no more dyspnea. The blood was brown red, and contained much less methemoglobin. The appetite was good, and the stools were normal in number and consistency. Blood, 30 c.c., was given again intravenously. Forty-eight hours after the first signs of illness, the symptoms were completely absent. There was no more methemoglobin present in her blood, and her skin had a normal color.

Laboratory Data.—Laboratory data at the time of admission to the clinic were as follows:

Blood: Hemoglobin, 75 per cent; white blood cell count, 45,000. Differential count: neutrophiles, 63; lymphocytes, 24; monocytes, 2; metamyelocytes, 9; plasmocytes, 2. A few toxic neutrophiles. The bone marrow smears were normal. The day after the first transfusion the white blood cell count was 18,000.

Urine, no abnormal findings.

Stools, no fat or starch or parasites.

Serum bilirubin, 0.68 mg. per cent.

The blood culture gave no growth.

Blood-urea 20 mg. per 100 c.c. Bleeding and coagulation times were normal.

We did not search for nitrites in the blood nor for nitrosobacilli in the stools.

The toxicologic analysis on the cough medicine and on samples of the milk powder gave negative results. The child did not wear clothes dyed with aniline.

From the Institut de Pédiatrie (Prof. L. Maldague) University of Louvain.

The well water used for the dilution of the formula contained 497 mg. NO_3 per liter and 0.114 mg. NO_2 per liter. The well was two meters away from the cesspool. Bacteriologic examination of the water revealed the presence of colibacilli and enterococci about 700 per c.c. The parents stated that the water was boiled before its use. No other members of the family were ill from this water. Following recovery of the patient, the well water was omitted from the baby's formula. We saw the child eight months later. Her growth was normal and uneventful and she looked perfectly well.

CASE 2.—D. O. was a girl 1 month of age. Her family and prenatal history were not contributory. Since birth she had received powdered milk diluted in well water in good proportions. When she was 15 days of age, she became suddenly rather cyanosed, but her general condition seemed to be good, and on the following day she regained her normal appearance. Five hours before this child was rushed to the hospital, the mother had noticed the appearance of a cyanosis considerably more marked than in the first episode. The infant had refused her feedings. Her stools were normal.

Physical Examination.—There was striking coloration of the skin and of the mucosae, quite similar to the former case in severity and in distribution. The pulse rate was 175 per minute. The respiration rate was 78. There was no movement of the alae nasi. Otherwise, the clinical examination was normal.

The venous blood was chocolate brown and contained large amounts of methemoglobin and about 100 gammas of nitrites per 100 c.c. The urine was normal. The blood contained 60 per cent hemoglobin, 2,660,000 red blood cells, 27,900 white blood cells. Differential count: neutrophiles 25, eosinophiles 4, lymphocytes 67, monocytes 3, myelocytes 1.

She was given intravenously 5 mg. of methylene blue dissolved in 5 c.c. of water, added to 20 c.c. of a 20 per cent glucose solution. The injection lasted fifteen minutes. One-half hour after the end of this injection, the tint of the skin, as well as the respiration and the pulse rate, returned to normal. The venous blood, which had then a normal color, contained no further methemoglobin. The white blood cell count was 13,800. She drank eagerly three bottles during the course of the night.

The child was discharged the next day.

Five days later, the patient was hurried again to the clinic. She had been quite normal at home, taking her feedings, having normal stools and normal color. During the preceding night she had cried a great deal and the mother had the impression that cyanosis was recurring. At daybreak she saw that the skin appeared as blue as it had during the former spell. By the time the child was seen she was in the seventh hour of the attack. The general condition being really alarming, caffeine was administered. An attempt was made to give methylene blue intravenously, but just as the injection was started, the patient died.

The blood removed just before the child's death was again found to contain large amounts of methemoglobin and about 100 gammas per 100 c.c. of nitrites.

Autopsy Report (Dr. J. Picard).—Good nutrition. Small intestine: normal. Colon: Throughout the sigmoid and in part of the rectum was found a large hemorrhagic, confluent ulceration with marked thickening of the intestinal wall. Spleen: normal volume, chocolate-like color. (This was the only evident sign of methemoglobinemia.) The other organs seemed to be normal.

Microscopic data: Spleen: Normal red and white pulp. In the red pulp numerous deposits of brown blood pigment. Liver: A few exudative foci scattered in the parenchyma, containing chiefly mononuclears. Kidneys: Normal. Colon: Ulceration of the mucosa, with marked congestion and interstitial hemorrhages in the submucous layer. The muscular layers appear to be normal.

The benzedrine reaction was positive in fecal material recovered from the colon and negative for that contained in the small intestine. Stool cultures were negative for nitrosobacillus. The well containing the water used for the dilution of the formula was two meters away from the cesspool.

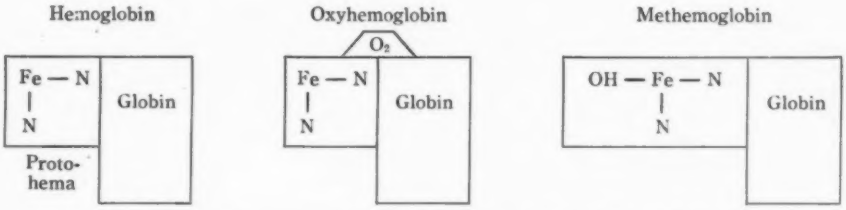
This water contained 180 mg. nitrate per liter, and traces of nitrite. The bacteriologic examination of this water revealed the presence of a few colibacilli.

No other members of the family appeared to suffer from the use of this water.

DISCUSSION

In the two cases recorded herein, diagnoses of bronchopneumonia, infantile cholera, and congenital malformation of the heart were ruled out, and the cyanosis was attributed to methemoglobinemia.

Methemoglobin[2] is an hydroxide of hemoglobin, in which the OH group is directly bound to the trivalent iron.



Several agents have the capacity of transforming, in vitro and in vivo, hemoglobin into methemoglobin (see further).

Methemoglobin is not toxic but is unable to transport oxygen. When two-thirds of the hemoglobin of a dog has been transformed into methemoglobin, the dog dies.[3] After the formation of methemoglobin, if the toxic agent is withdrawn, spontaneous transformation of the methemoglobin into normal hemoglobin occurs.[1] This transformation is almost complete after thirty-six hours.[3] In the first hours after death, a part of the hemoglobin is converted into methemoglobin. Recent work has shown that methemoglobin is a normal constituent of human blood in the proportion of 1 per cent.[3a]

From the clinical point of view, methemoglobinemias can be classified in two groups:

1. *The first group* includes the plasma methemoglobinemias. Here there is no methemoglobin in the red blood cells. But after hemolysis of a part of the red blood cells, the hemoglobin of the corpuscles dissolves in the plasma and is transformed into methemoglobin. It can occur in eclampsia, in blackwater fever, in paroxysmal hemoglobinuria, in sepsis due to anaerobic organisms, in Winckel's disease and others. The latter disease has several synonyms: cyanosis afebrilis icterica, maladie bronzée hématurique de Parrot, etc. It occurs by epidemics in newborn infants of six to thirty days and is characterized by cyanosis, icterus, hemolysis, and methemoglobinuria.[4-8] The methemoglobin of our patients was present exclusively in the cellular elements. Therefore, their disease cannot be classified in this first group.

2. *The second group* includes the cellular methemoglobinemias. When no toxic agent can be detected, one speaks of enterogenic or idiopathic cyanosis. This disease was first described by Stokvis[9] and by Talma[10] in 1902. The cyanosis is slowly progressive and the patient has only digestive troubles: chronic diarrhea or constipation, with or without abdominal pain. Hymans van den Bergh[11] has shown that the blood of several patients with this disease contained nitrites. Other workers[12] found nitrosobacilli in the stools and saliva of the patients.

Included among the toxic agents able to induce methemoglobinemia are the sulfonamides, aniline, nitrobenzenes, acetanilide, nitrites, bismuth subnitrate, potassium chlorate.

In the literature of the subject, the first case reported in an infant was published in 1940 by Schwartz and Rector.[13] Their patient was a girl 2 weeks old, whose familial history was not contributory. She lived in the country and was fed with a formula made with powdered milk. At 9 days of age the parents observed that the child had become deeply cyanotic. After three days, without any treatment, the color of the skin gradually became normal except during crying. On the fifteenth day of life her skin became rapidly cyanotic, and she was rushed to the hospital. Physical examination gave negative results except for the highly abnormal color of the skin. The white blood cell count was 30,000 and the blood contained 57 per cent methemoglobin. Three mg. of methylene blue per kilogram of body weight were administered intravenously. In one-half hour the cyanosis had completely disappeared. Following this episode there was no recurrence of symptoms. Nitrosobacilli in the stools, nitrites in the blood, and nitrates in the water used for dilution of the powdered milk were not sought. The authors did not report whether or not the formula was changed after the stay of the child in the clinic.

In 1945, Comly[14] discovered the etiologic process. In his paper he presented two of his own cases and discussed several others, similar in nature, verbally communicated to him by other physicians. The following conclusions were made by Comly:

1. The disease occurs in infants of less than 2 months.

2. These children live in the country and are fed powdered milk diluted in well water. The well water employed in the children's diet contains nonpathogenic microbes, significant amounts of nitrates and small amounts of nitrites:

In his first case	619 mg. ion NO_3	per liter
	0.4 mg. ion NO_2	per liter
In his second case	388 mg. ion NO_3	per liter
	1.3 mg. ion NO_2	per liter

3. The first patient had three attacks of methemoglobinemia followed by complete recovery after withdrawal of the well water from the formula.

4. The adults drinking the same water were not sick and their blood contained no pathologic amounts of methemoglobin. The amount of water that they drank was relatively much less than for the infants.

5. Each attack of methemoglobinemia was completely cured with methylene blue.

Unfortunately he did not look for nitrites in the blood of the patients during the attacks.

The following question is now in order: are relatively small amounts of nitrates responsible for such accidents? Let us compare all those patients' histories with the fatal attacks of methemoglobinemia occurring after administration of bismuth subnitrate by roentgenologists, in administering contrast media,

or by physicians as a therapeutic agent for enteritis. The following cases are reported by Roe:[15]

1. An infant, 1 month of age, had been receiving bismuth subnitrate for a refractory enteritis. After twenty-four hours of treatment, in which 7 Gm. of the drug had been given, a marked cyanosis appeared. After forty-eight hours, the child was strangely cyanosed. The drug was then stopped. By this time the child had taken 13 Gm. of bismuth subnitrate. He died twenty-four hours later with cyanosis and hypothermia. At post-mortem no characteristic lesion was found. Blood analysis showed that the cyanosis was due to corpuscular methemoglobinemia.

2. An infant, 3 weeks old, suffering from enteritis, had been given 3 Gm. of bismuth subnitrate by gavage for x-ray purposes. The child died twelve hours later, with strong cyanosis due to methemoglobinemia.

The other cases of Roe will not be discussed because of lack of laboratory data.

It is obvious that the toxic element was the NO_3 ion, for such accidents have never been reported after administration of another bismuth salt.

In Table I the amount of NO_3 ion absorbed by our patients and by the patients of Comly is converted into the corresponding amount of bismuth subnitrate, and compared to the amount of the drug ingested by the patients reported by Roe.

TABLE I

REPORTED BY	CASE	AGE	MG. IONS NO_3/l	CORRESPONDING AMOUNT OF BISMUTH-SUBNITRATE		DIARRHEA
				TOTAL AMOUNT (GM.)	AMOUNT (GM.) PER DAY	
Ferrant	1	1 mo.	497	30	1.5 during 21 days	+
	2	1 mo.	180	14	0.5 during 21 days	–
					0.6 during 6 days	Ulceration of the sigmoid colon
Comly	1	1 mo.	619	19	2.7 during 2 days	–
					2.7 during 2 days	–
					2.7 during 2 days	–
	2	1 mo.	388	35	1.1 during 30 days	+
Cases of Fatal Intoxication With Bismuth Subnitrate						
Roe	1	1 mo.		13	6.5 during 2 days	+
	2	3 weeks		3	3.0 during 1 day	+

In accordance with the similarity observed in Table I, it seems logical to conclude that the methemoglobinemia of our patients and of the patients of Comly was due to the nitrates in the well water. Similar amounts of NO_3 ion from bismuth subnitrate introduced into the intestinal tract of infants with diarrhea induced fatal attacks of methemoglobinemia. In our second case there was no diarrhea, but at post-mortem a large ulceration of the sigmoid colon was unexpectedly found. It is possible that the same lesion occurred in the second patient of Comly.

The *mechanism* of the toxic action of the NO_3 ion will now be discussed.

Normally, during digestion, nitrates are produced in the intestinal tract. These are not absorbed but are reduced to nitrites and then to ammonia. When relatively large amounts of nitrates are ingested by a child suffering from accelerated intestinal transit and inflammation of the mucosa, it is possible that the nitrites have no time to be completely reduced and that, through this defective mucosa, they are able to reach the circulating blood. Nitrites are catalytic agents. It is quite abnormal to find them in the blood. It remains to be proved by dog experimentation whether amounts of nitrites of about 100 gammas per 100 c.c. are able to induce abrupt attacks of methemoglobinemia.

There are other evidences to sustain this pathogenic hypothesis.

1. In idiopathic cyanosis there are digestive disorders and Hymans van den Bergh found nitrites in the blood of a few patients.

2. The digestive mucosa of the child is normally more delicate than that of the adult.

3. In infants the metabolism of fluids is more rapid and more important.

4. The nitrates are introduced in the ingested water, which is polluted by potentially pathogenic microorganisms.

The former *treatment* of the methemoglobinemias consisted of blood withdrawal and transfusion, oxygen therapy, and rest of the gastrointestinal tract.

The use of methylene blue represents a successful innovation.[16] Methylene blue, which is a very efficient reducing agent, increases the combustion of oxygen by the human erythrocyte some twenty to thirty times. On the other hand, methylene blue is considered to be the antidote of hydrocyanic acid.[17] Favorable results have also been claimed for methylene blue in the treatment of sulfhemoglobinemia.[18-21] Its beneficial action in carbon monoxide intoxication is questioned by many.[22] The clinically active dose is 1 to 2 mg. per kilogram of body weight. When rapid action is desired, it may be administered intravenously. In chronic cases it is given by mouth. Some authors object to the use of methylene blue in that it has the property of transforming, in vitro, hemoglobin into methemoglobin. Methylene blue itself is transformed into the leuco form, which in turn reacts with oxygen and forms again methylene blue.

$$\text{Hemoglobin} + \text{Methylene blue} \rightarrow \text{Methemoglobin} + \text{Leuco form}$$
$$\text{Leuco form} + \text{Oxygen} \rightarrow \text{Methylene blue}$$

At first sight it seems illogical to administer a methemoglobin-forming agent to patients suffering from methemoglobinemia. But clinical experience forces us to accept what biologists are unable to explain. Several theories have been proposed, none of which can be regarded as conclusive.

Other harmful effects of methylene blue have been pointed out: anxiety, obsession, paresthesias, depressing action on respiratory and circulatory centers. But to obtain such untoward symptoms one must inject amounts far greater than those usually administered. Brooks[23] advises that methylene blue be dissolved in hypertonic glucose solution because in vitro glucose transforms methemoglobin into oxyhemoglobin. Ascorbic acid and niacin possess the same property.

Lederer[24] advises the replacement of methylene blue by thionine, a violet dye, not toxic and not methemoglobin formative, which has a reducing power five times greater than that of methylene blue. Hauschild[25] used methylene blue and thionine with comparable results. In our cases, thionine was not employed because it was unobtainable.

CONCLUSIONS

The incomplete modernization of rural districts frequently makes it necessary for the inhabitants to resort to the use of well water containing excessive amounts of nitrates for the diluting of powdered milk feedings. These nitrates are probably considerably more toxic for newborn infants than for adults, especially if the infants have a digestive disorder.

It is probable that nitrates are transformed in the intestinal tract into nitrites, which in turn are resorbed and act in the blood stream as a methemoglobin-forming agent.

The outstanding feature in the clinical picture is the contrast between the cyanosis and the alarming condition of the patient on the one hand, and the normal aspect of the respiratory and circulatory system, on the other. The anoxemia, which results from the high level of methemoglobin in the blood, explains the shock, polypnea, dyspnea, tachycardia, and prostration. Diarrhea may be present. The color of the blood varies from brown red to brown black. There is no hemolysis and the methemoglobin is corpuscular. On the average, the methemoglobin level in the blood seems to be above 50 per cent of the total pigment. The white blood cell count during attacks is elevated.

In our second case, blood drawn during the attack contained about 100 gammas of nitrite per 100 c.c. We strongly suggest similar investigations in related cases.

At autopsy in the second case, large ulcerations of the mucosa of the sigmoid colon were found. The other organs appeared to be normal.

Treatment must be instituted quickly. The toxic agent must be immediately withdrawn, and transfusions are certainly in order. However, methylene blue (1 or 2 mg. per kilogram of body weight) is effective and seems to be free from risk.

The prophylaxis of such accidents is the concern of the Public Health Department.

SUMMARY

Two cases of methemoglobinemia in newborn infants are presented. They appeared to be caused by nitrates in the well water used for the dilution of powdered milk in the formula.

In the first case, the acute stage was successfully treated with transfusions.

In the second case, the first attack was healed by methylene blue. However, treatment was begun too late to save the patient in a second attack.

The literature of the subject is briefly reviewed.

The pathogenesis of the disease is discussed in connection with the finding of large amounts of nitrates in the well water and of small amounts of nitrites in the blood of the second patient.

We thank Professor Louis Maldague for permission to publish the cases from his service. We also thank Mr. Jules Ladenheim for help in the translation. We are indebted to Mr. J. Steenhoudt, who made the chemical and spectroscopic analyses, to Dr. Piet de Somer for bacteriologic determinations and to Dr. Joseph Picard for the pathologic data.

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METHEMOGLOBINEMIA OCCURRING IN INFANTS FED MILK DILUTED WITH WELL WATER OF HIGH NITRATE CONTENT

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THIS report concerns two newborn infants with proved methemoglobinemia successfully treated with injections of methylene blue and a third infant who probably had methemoglobinemia and recovered spontaneously. The methemoglobinemia in all three of the infants was associated with the ingestion of milk mixtures diluted with well water containing a large amount of nitrate ions.

Our attention was directed to these observations by a recent article by Comly[1] describing the occurrence of methemoglobinemia in several infants in Iowa under similar circumstances. He has hypothesized that the ingested nitrate is reduced to nitrite by the intestinal flora and that the absorbed nitrite then changes hemoglobin to methemoglobin. Irrespective of whether or not Comly's theory is correct, the facts regarding the ingestion of milk mixtures diluted with well water of high nitrate content are uniformly present both in his series of infants and in ours.

REPORT OF CASES

CASE 1.—J. K., white male infant, 4 weeks of age, was admitted to the University of Kansas Hospitals at 10 A.M., Dec. 30, 1945, from Louisburg, Kan., because of cyanosis and drowsiness. The infant was the firstborn of twins who were delivered after a pregnancy of eight months. The birth weight was 5 pounds, 8 ounces. After delivery he was resuscitated with some difficulty. At the age of 3 days he was placed on a dilute milk-mixture containing 10 ounces of evaporated milk and 20 ounces of boiled water with 5 per cent carbohydrate added. Three ounces were offered every four hours. He remained in the hospital for thirteen days and is said to have become cyanotic when he cried during this time. After he left the hospital, the cyanosis increased in frequency and severity, and was constantly observed to be present by the time he was 3 weeks old. He became progressively more lethargic and listless, and at 3 A.M. on the day of admission he became very deeply cyanosed and very listless. The intensity of the cyanosis had diminished before admission, but the infant was still very lethargic and cyanotic when the decision was made to bring him to the hospital.

Physical examination revealed a poorly nourished infant weighing 2,525 Gm. with a peculiar bluish gray discoloration that was not typical of true cyanosis. The fontanel did not bulge, the neck was not stiff, there was no lymphadenopathy and the pharynx was normal. The breath sounds were normal and equal on both sides. No râles were heard. The respiratory rate was 60 per minute. No dullness to percussion could be made out over the lung fields. The heart was not enlarged. There was a soft systolic murmur which was heard best at the apex. No thrills or arrhythmia were noted. The heart rate was 132 per minute. The examination of the abdomen, genitals, and extremities was entirely negative. The infant was given oxygen by nasal tube, but no improvement in the cyanosis was noted.

Methemoglobin and hemoglobin concentrations were determined by the method of Evelyn and Malloy.[2] When the blood was drawn for these determinations, it was markedly chocolate in color. The methemoglobin concentration was 6.7 Gm. per 100 c.c. of whole blood.

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The hemoglobin concentration was 11.5 Gm. per 100 c.c. of whole blood. This left only 4.5 Gm. of functioning hemoglobin per 100 c.c. of whole blood. Five-tenths cubic centimeter of 1 per cent methylene blue was given intravenously and within one-half hour the baby's color was normal, respirations were 30 per minute and he was clinically well. The methemoglobin concentration in the blood one-half hour after the administration of the methylene blue was 0.4 Gm. per 100 c.c. of whole blood.

Further laboratory work showed the urine to be negative. The red blood cell count was 4,260,000 per cubic millimeter. The white blood cell count was 22,700 per cubic millimeter. The differential white blood cell count was normal. Roentgenograms of the chest showed the lungs to be clear and the heart to be normal in size and shape.

Two days later the infant had mild generalized clonic convulsions. The nonprotein nitrogen was 36.6 mg. per cent; the calcium was 10.9 mg. per cent and the blood sugar was 91 mg. per cent at this time. These convulsions became less and less severe and after three days stopped altogether. It was thought that these were probably due to cerebral anoxemia associated with the low amount of functional hemoglobin found on admission. At the time of discharge eight days after admission, the baby weighed 2,815 Gm.; he had a normal color and showed normal activity.

CASE 2.—J. K., female twin sibling of J. K. (Case 1), was born four hours after her brother. She was admitted to the University of Kansas Hospitals at 2 P.M. on Dec. 30, 1945, with the same complaints as her twin brother.

At birth this infant had weighed 7 pounds and 5 ounces and had always been stronger than her sibling, but on numerous occasions she had, since dismissal from the hospital where she was born, become cyanotic around the lips. She had had slight episodes of listlessness, but on the day before admission she became very cyanotic and lethargic. Since the third day of life she had been offered every four hours 3 ounces of a milk mixture containing 10 ounces of evaporated milk, 20 ounces of water and 1 ounce of syrup.

Physical examination on admission showed a lethargic but not comatose infant weighing 3,220 Gm. The skin had the same peculiar bluish gray discoloration as that of her twin and was not relieved by oxygen inhalations. The respiratory rate was 64 per minute. The pulse rate was 168 per minute. The physical examination otherwise was entirely negative.

Laboratory examination showed a total hemoglobin of 13.5 Gm. per 100 c.c. of whole blood and a methemoglobin concentration of 9.6 Gm. per 100 c.c. of whole blood, leaving 4.3 Gm. of functioning hemoglobin per 100 c.c. of whole blood. The blood was the same pronounced chocolate color as noted in Case 1.

The infant was given 0.6 c.c. of 1 per cent methylene blue intravenously. Twenty minutes later the baby's color had become normal; the respiratory rate had dropped to 40 per minute and the pulse rate was 130 per minute. One-half hour after the methylene blue was given, the methemoglobin concentration was 0.7 Gm. per 100 c.c. of whole blood.

The infant seemed perfectly well thereafter and was dismissed on the eighth hospital day weighing 3,375 Gm.

The water used in making the milk mixtures for this set of twins was obtained from a well dug on the premises. Chemical analysis by the Division of Public Health Laboratories of the Kansas State Board of Health showed that the well water contained 70 mg. of nitrate nitrogen and only a trace of nitrite nitrogen per liter.

CASE 3.—A third infant, F. K., was admitted to the University of Kansas Hospitals from Greely, Kan., on July 25, 1945, because of cyanosis, which in retrospect we believe was the result of an excessive methemoglobinemia.

This infant was 2 weeks old when admitted. Five days before admission this infant became blue, and when he cried the cyanosis was greatly exaggerated. There was no respiratory embarrassment and the baby continued to eat and sleep well. The bluish discoloration continued until admission. This infant was born at home and weighed 8 pounds and 8 ounces at birth. He never was breast fed but was given a milk mixture containing one part Similac and two parts of boiled water. He also was given water between feedings.

Physical examination showed an active infant weighing 3,850 Gm. The skin was bluish gray in color. There was no dyspnea or tachypnea. The pulse rate was rapid. There was no cardiac enlargement and no thrills. A faint systolic murmur was heard over the pulmonic area. The lungs were clear to auscultation and percussion and the rate was not abnormally rapid. The liver was palpable 4 fingerbreadths below the right costal margin. The remainder of the physical examination was entirely negative.

Laboratory examination showed the urine to be negative. The red blood cell count was 4,880,000 per cubic millimeter. The white blood cell count was 10,700 per cubic millimeter with a normal differential. There was 13.5 Gm. of hemoglobin per 100 c.c. of whole blood. Methemoglobin determinations were not made. The calcium level was 12.1 Mg. per cent. Roentgenograms of the chest showed the lungs to be clear and the heart normal in size and shape.

Oxygen was administered but it did not decrease the cyanosis and hence was discontinued. The cyanosis gradually diminished and by the end of the first week in the hospital it had disappeared completely. The patient was discharged on the eighth hospital day apparently entirely well.

Water was obtained from the well used by the family and was tested by the Division of Public Health Laboratories of the Kansas State Board of Health. The water was found to contain 300 mg. of nitrate nitrogen and a trace of nitrite nitrogen per liter.

COMMENT

The methemoglobin concentrations in the blood of the twins in this report were much higher than those found by Comly in the group of infants in Iowa. The higher concentrations obtained in the twins reported here probably were the result of an earlier recognition of the condition. In Comly's series the infants remained in the hospital several days before methemoglobin determinations were done, thus permitting a certain amount of spontaneous recovery to occur. The concentration of methemoglobin in the blood probably diminishes rapidly in a period of four or five days if the infants are fed milk mixtures that are free of nitrates. The infant in the present report on whom determinations were not made for methemoglobin probably is an example of the spontaneous cure that can result if the infant is placed on undiluted cow's milk.

Death has been reported as a result of severe methemoglobinemia. It seems possible that these infants might have had a fatal outcome if further reduction of functional hemoglobin had occurred. It is surprising that they could have survived with their functional hemoglobin reduced to as low as 4.3 Gm. per cent.

The amount of nitrate ingested in relation to body weight apparently is the determining factor as to whether clinical methemoglobinemia develops or not. All adults drinking water from the well supplying the twins reported here were tested for methemoglobinemia and none was found. A 6-month-old infant, who lived in the same house and who has been fed a milk mixture made with the same water since birth, has never exhibited any signs of methemoglobinemia. However, his formula was made with equal parts of whole cow's milk and boiled water. For this reason his ingestion of nitrate ion has probably been proportionately less. For this reason it would seem wise to feed infants living on farms, when the character of the water is unknown, milk mixtures which are fairly concentrated or made with water obtained from a source known to be satisfactory.

The use of methylene blue in the treatment of this condition has been well reviewed by Comly; in our cases its effect was dramatic and left nothing to be desired.

The geographical distribution of cases of methemoglobinemia associated with the ingestion of well water containing large amounts of nitrate ions has been extended to include Kansas as well as Iowa. It is likely that the location and condition of wells dug in many rural areas in other states are such as to permit the contamination of the water by seepage from barnyards and other sources high in nitrogenous materials. If such is the case, it would be expected that methemoglobinemia might be encountered over wider areas than has yet been reported, particularly since the feeding of milk mixtures and products requiring relatively large amounts of water is probably widespread.

Methemoglobinemia in newborn infants as the result of absorption of aniline dye from newly stamped and unlaundered diapers has been reported.[3] Consequently it is important to bear in mind that the ingestion of contaminated well water is not the only factor which can produce methemoglobinemia in this age group.

SUMMARY

1. Two cases of proved methemoglobinemia in newborn infants probably caused by the ingestion of water with a high concentration of nitrate ion are reported. A third case of suspected methemoglobinemia from the same cause is also added.

2. The efficacy of methylene blue in the treatment of this condition is corroborated.

3. It is suggested that special precautions be taken in rural areas to see that any water used in the feeding of infants is safe in respect to its nitrate content.

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THE DIAGNOSIS OF ABORTIVE POLIOMYELITIS

A Study of Illnesses Occurring in 1,123 Contacts of Patients With Poliomyelitis

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IN THE older writings on poliomyelitis, the essential criterion for making a diagnosis was the finding of flaccid paralysis in one or more muscle groups. However, since the classical studies of Wickman[1] it has been evident that in addition to paralytic cases, there are also individuals who pass through the acute early symptoms of the disease but never progress to the point of muscle paralysis. These have been called nonparalytic or abortive cases. Patients with this form of the disease may show signs of meningeal irritation and changes in the spinal fluid similar to those of the paralytic cases, but the course is likely to be milder and of shorter duration. At the present time, most physicians are able to recognize nonparalytic cases and to care for them adequately from the public health viewpoint. Unfortunately, the problems of diagnosis and control involve a far larger number of individuals than are represented by the paralytic and the diagnosed nonparalytic cases. Until the extent of dissemination of the virus in a community is better known, and until the nature of the mild symptoms caused by the infection is more widely appreciated, measures directed toward the control of epidemics can be of little value.

It is an almost universal observation of physicians who have worked intimately with an epidemic of poliomyelitis that during such a period many individuals are ill with clinical symptoms of an entirely nonspecific nature but which appear to be related in some way to the epidemic itself. The closeness of the association between such individuals and recognized paralytic cases may suggest that the etiologic agent is the same. On the other hand, the clinical picture shows nothing on which to base the diagnoses. Even the findings in the spinal fluid are not necessarily characteristic, for although an increase in the number of cells is occasionally found, this is unusual and not the expected result. Furthermore, studies of the distribution of the virus at the time of an outbreak of the disease have shown many individuals to be infected who had only mild and brief symptoms, or even none at all.[2] In the absence of more exact methods for making a diagnosis of infection with the virus of poliomyelitis, the problems facing the practicing physician are difficult and confusing. On the one hand, if he makes the diagnosis only on the basis of paralysis or changes in the spinal fluid, a large number of individuals will be circulating in the community and spreading the virus among their intimate friends. On the other hand, to label every minor or suspicious illness as a case of poliomyelitis may arouse unjustifiable alarm in the family and community. Until the time arrives when confirmation of a suspected diagnosis can be quickly and accurately obtained

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by laboratory procedures, the physician must rely on his own experience and judgment, and no uniform policy can be expected.

As an aid to the recognition of early and mild cases of the disease, it seems necessary to obtain a clear picture of the clinical symptoms which might be expected. Although numerous reports have pointed out the general characteristics of "abortive poliomyelitis,"[2] the studies carried out during the 1944 outbreak in the Buffalo, N. Y., area, offered an unusual opportunity to amplify and extend the information.

STUDY MATERIAL

As part of an epidemiological study of the reported cases of poliomyelitis in the Buffalo, N. Y., area, during the summer of 1944, detailed investigations of activities and contacts were made in approximately 900 cases. The methods of investigation have been described elsewhere.[3] In 194 of these individuals, the epidemiological data obtained were too inadequate to be used. However, in 504 instances, one or more individuals with whom the patient had been in close contact had been ill during the general period of the patient's disease, with symptoms which had not been diagnosed as poliomyelitis. In some, this illness had occurred from one to three weeks before the onset of the poliomyelitis and could have been a possible source of the virus; in others, it occurred simultaneously, suggesting a common source; and in still others, it occurred from one to three weeks afterward and was interpreted as a secondary illness probably acquired by contact. Whenever possible, the descriptions of these illnesses were amplified by visits to the homes concerned. The actual number of associated illnesses, including twenty-nine cases of poliomyelitis, was considerably larger than that finally used in the study. Many, however, were excluded because of uncertainties regarding the closeness of the contact. There remained 1,123 instances in which circumstances pointed to the likelihood of the associated illnesses being caused by the same agent which was responsible for the patients' diagnosed poliomyelitis. The following report is based on an analysis of these associated illnesses.

This group of illnesses was selected for study because, on circumstantial evidence, they would be assumed to be caused by the virus of poliomyelitis regardless of the symptoms presented. Such an assumption is, of course, open to the criticism that no positive proof can be offered that every illness was actually caused by the virus. However, in selecting the illnesses from the information at hand, care was used to exclude any in which the contact with the paralytic case was either vague or indirect. Furthermore, as shown in Tables I and II, approximately 50 per cent of the individuals with minor illnesses were members of the immediate family of poliomyelitis patients—parents, siblings, and grandparents. Playmates, friends, and neighbors comprised an additional 40 per cent. The remaining 10 per cent was made up of aunts, uncles, cousins, and other relatives. The closeness of the relationship to the patient added to the probability of a common infectious agent being responsible for all. While not necessarily conclusive, the circumstantial evidence points strongly toward the poliomyelitic nature of the illnesses of these individuals.

RESULTS

The types of illnesses encountered among the group varied widely. In some instances, another case of the disease was diagnosed. Others were sick with fever, vomiting, headache, and painful extremities, symptoms which persisted for a week or longer and were followed by a prolonged period of convalescence. Such illnesses are suggestive of undiagnosed nonparalytic poliomyelitis. In still others, the only symptom consisted of a running nose, a day

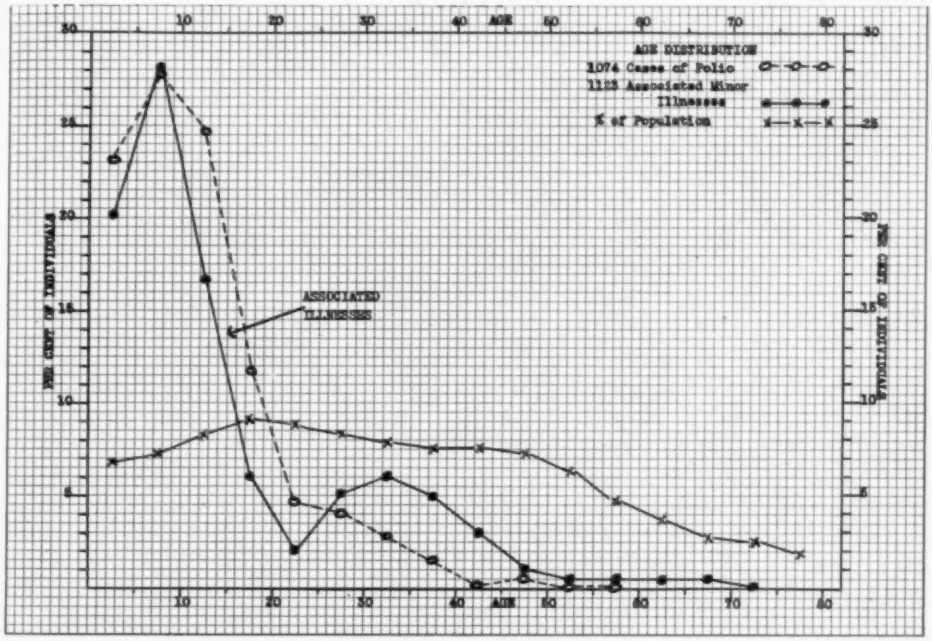

Fig. 1.—Age distribution curves of 1,074 reported cases of Poliomyelitis, 1,123 associated minor illnesses, and of the general population.

of indisposition, a sore throat, or a period of nausea and vomiting. Except for the group which showed meningeal or paralytic symptoms, the descriptions rarely contained any criteria from which a distinction could be made between a

TABLE I. RELATIONSHIP OF INDIVIDUALS HAVING MINOR ILLNESSES TO POLIOMYELITIS PATIENTS

RELATIONSHIP	NUMBER IN IMMEDIATE FAMILY	TOTAL NUMBER OF ILLNESSES	PERCENTAGE
Parents	197		
Siblings	342		
Grandparents	13	552	49
Neighbors, friends or playmates		445	40
Cousins, aunts, uncles		114	10
Others		12	1
Total		1,123	100

TABLE II. NATURE OF THE CONTACT BETWEEN DIAGNOSED CASES OF POLIOMYELITIS AND 1,123 INDIVIDUALS WHO HAD MINOR ILLNESSES

NATURE OF CONTACT	NUMBER	PERCENTAGE
Household	559	50
Neighborhood	408	36
Casual	156	14
Total	1,123	100

mild poliomyelitic infection and one caused by common pathogens. Several illustrations may help to visualize the type of illnesses encountered.

EXAMPLE I.—About August 1, a playmate of the patient had a sore throat, "cold," and fever which were thought by the family to represent a "mild case of infantile paralysis." The patient, an 8-year-old boy, developed poliomyelitis of the bulbar type with indefinite symptoms beginning on August 10, throat paralysis on August 12, and death four days later. On August 21 and 22, three of the patient's siblings, aged 3, 5, and 12 years, were ill with fever and vomiting. In one of these, mild weakness in the muscles of one leg was discovered several weeks later. On August 25, another sibling of 6 years had a similar episode of fever and vomiting. The mother, who had been away from home from August 5 to 16, returned on this latter date to care for the patient. On August 30, she complained of a sort throat, headache, and pains in the legs which persisted for several days. All four members of a neighboring family were also ill with fever and vomiting at about the same time, although no definite dates could be established.

In this group, gastrointestinal symptoms seemed to predominate, but three individuals had other symptoms which suggested true poliomyelitis in a mild and nonparalytic form.

EXAMPLE II.—During the epidemic this family was so apprehensive that the members left town and spent the summer with relatives 200 miles away. They returned on September 18 to a neighborhood in which there had been several cases of poliomyelitis and many minor and apparently nonspecific illnesses. Upon arrived, the 11-year-old girl in the family was greeted by neighbors, aged 3 and 5 years, both of whom had profuse nasal discharges called "colds." On September 28, ten days after this contact, the 11-year-old child developed a watery nasal discharge and a little pain in head and eyes. However, she continued to play actively until October 2, when acute meningeal symptoms developed and the clinical diagnosis of poliomyelitis was confirmed by lumbar puncture.

The patient was in the habit of hugging and kissing her two smaller siblings each day. On October 12, fourteen days after the oldest child first developed symptoms, both younger ones had a "nose cold" with watery discharge which lasted from one to two days and subsided without complications.

Rhinitis was apparently the leading symptom in this group.

EXAMPLE III.—This family with eight children lived in a rural village in which several cases of poliomyelitis developed at a time when minor illnesses were prevalent. The father worked beside a man whose wife had poliomyelitis beginning on July 4, but neither man admitted symptoms of any kind. On August 8, the 14-year-old child complained of nausea and sore throat which lasted two days. On the following day, the 4-year-old child acted sick and had no specific symptoms, but ten days later he complained of sore legs and limped for a time. On August 13, a 7-year-old child complained of nausea, headache, and a slight fever for two days. Another child of 2 years was irritable and refused to eat for the single day of August 16. On August 17, the mother had chills and fever, sore throat, pains in back of the neck and legs, and could not walk comfortably. Two days later she felt well. On August 22, a 10-year-old child had prodromal symptoms of headache and mild fever with acute meningeal symptoms developing on August 27 and progressing to paralytic poliomyelitis. A 12-year-old child had nausea, malaise, and probably fever on August 31

and September 1. The two other children, aged 3 weeks and 6 years, had no symptoms of any kind as far as the parents could recall.

In this family, the mother and six of her eight children were ill within a period of three weeks. Only one of these illnesses was diagnosed as clinical poliomyelitis.

EXAMPLE IV.—During the early phase of the epidemic, several illnesses occurred in boys belonging to a local troop of Boy Scouts. One of these was diagnosed as possible bulbar poliomyelitis on June 26. An intimate friend, aged 12, developed a sore throat on July 3 and felt poorly for several days. On July 4, this latter boy spent the day with his sister, aged 8, and grandfather, aged 65. The sister become acutely ill with a mild bulbar poliomyelitis on July 16, and at the same time the grandfather developed an acute sore throat.

Related to this patient with bulbar poliomyelitis were a brother, aged 13, and a grandfather, aged 65, both of whom had illnesses characterized particularly by symptoms referable to the throat.

SYMPTOMS

In order to obtain a picture of the dominant symptoms of the entire group of 1,123 individuals, these are presented in Table III. Since the descriptions were obtained by interview and not by observation, the terms used correspond in so far as possible to the objective facts stated. Those described as stiff neck and back, headache, nausea and vomiting, sore throat, and diarrhea can be relied upon. The term "cold," however, is less definite in significance, for while it usually designates a respiratory infection involving the nose, among the less educated part of the population it is sometimes used to indicate a sore throat, a "cold in the bowels," fever with aches and pains. Although the terms used in the table are necessarily of limited significance as descriptions of the entire illness, they nevertheless indicate the symptoms which attract attention in average homes and represent the basis from which the practicing physician and health officer must work. The symptoms have been arranged in the order of decreasing suspicion of poliomyelitis. Other symptoms which occurred in combination with those higher in the list were excluded from the counts in the lower part. Thus, although meningeal symptoms, described as stiff neck or back, and pains or weakness of the extremities, were encountered less frequently than others, because these were most suggestive of true poliomyelitis, they were placed first in the table. Headache, which was usually persistent, was placed next. Because of the uncertainty of the significance of the term "fever," this was given a somewhat lower place. A hierarchy of single major symptoms of each individual was thus set up, in which less important symptoms appearing in combinations were relegated to lower positions.

The table demonstrates that a large majority of the individuals lack symptoms that would indicate to a physician a specific involvement of the central nervous system. Thus, in only 19 per cent of the group was there either stiff neck, stiff back, weakness of the extremities, or painful extremities. Usually such symptoms disappeared in from twenty-four to forty-eight hours without sequelae, but occasionally they persisted for from five to seven days. In the great majority—over 80 per cent—the illnesses had no characteristics which could distinguish them from diseases of an entirely different nature. Thus the

nonspecific nature of so many of the symptoms emphasizes the inadequacy of clinical methods for making a diagnosis of infection with the virus of poliomyelitis, and in the absence of a simple confirmatory laboratory test, epidemiological facts may offer helpful guides.

In most instances, more than one symptom was described for each illness, and combinations of all kinds were seen. While fever with nausea and vomiting was encountered most frequently, the combination of fever and sore throat with or without vomiting was also common. The duration of the individual symptoms and of the total illness varied greatly. In many instances they were transient, and the individual felt well within from twenty-four to forty-eight hours. In others, the symptoms persisted for a week with slow convalescence. The clinical picture was in no way consistent, although certain patterns were encountered more frequently than others.

TABLE III. FREQUENCY OF DOMINANT SYMPTOMS OF 1,123 CLOSE CONTACTS OF PATIENTS WITH DIAGNOSED POLIOMYELITIS

SYMPTOMS	NO. OF INDIVIDUALS	PER CENT OF TOTAL
Stiff neck and back	97	9
Extremities weak and painful	111	10
Headache	10	1
Nausea and vomiting	324	29
Sore throat	217	19
Fever	162	14
Other symptoms	202	18
Total	1,123	100

COMPARISON WITH EARLY SYMPTOMS OF DIAGNOSED CASES

The term "abortive poliomyelitis," which is in common use, connotes an illness which begins as the true disease but enters the recovery phase before the usual clinical characteristics appear. The minor illnesses which have been discussed should, theoretically at least, be similar to the initial stages of the disease itself. Wilson[4] has tabulated the early symptoms of the disease, but because of the possibility of variation from epidemic to epidemic it seemed desirable in the epidemic under discussion to compare the symptoms encountered among the contact illnesses with both the preparalytic symptoms of individuals who later developed paralysis and with diagnosed nonparalytic cases as well. In all, data from 334 paralytic and 137 nonparalytic cases were studied for comparison with the 1,123 contact illnesses. The results are presented in Table IV.

A similarity between the three groups can be seen in the table. Fever, nausea and vomiting, and sore throat were prominent in all. Meningeal and central nervous system symptoms were, of course, less common among the associated and undiagnosed minor illnesses. In addition, fever was less consistently present among the minor illnesses, which probably indicates nothing more than a milder degree of infection. In other respects the general character and proportion of symptoms in the three groups were similar. It should be pointed out that the differences between the two groups of diagnosed cases may not be significant, since the period of time from which the preparalytic

symptoms were drawn was short in contrast to the entire course of the non-paralytic cases. However, since the diagnostic problem of the physician is difficult only in the absence of paralysis, for the purposes of the present discussion the data as presented in the table seem most pertinent. In general, the facts suggest that the systemic manifestations of infection are similar in the three groups: if the disease fails to progress, evidences of involvement of the central nervous system are minimal.

TABLE IV. FREQUENCY OF SYMPTOMS ENCOUNTERED AMONG 1,123 CLOSE CONTACTS OF PATIENTS WITH POLIOMYELITIS AS COMPARED WITH THE SYMPTOMS OF DIAGNOSED HOSPITALIZED CASES OF THE DISEASE BEFORE PARALYSIS DEVELOPED OR IN CASES WHICH DEVELOPED NO TRUE PARALYSIS

SYMPTOMS	CONTACT ILLNESSES (%)	KNOWN CASES OF POLIOMYELITIS	
		PRECEDING PARALYSIS (%)	WITHOUT PARALYSIS (%)
Fever	49	80	82
Nausea and vomiting	36	49	58
Sore throat	29	21	24
"Cold"	21	10	11
Headache	16	55	63
Diarrhea	11	5	5
Cough	2	0	4
Drowsiness	1	10	14
Dizziness	1	4	11
Other	3	1	1
Symptoms referable to central nervous system			
Stiff neck and back	8	86	100
Extremities	13	37	50
Bulbar symptoms	0	5	10

AGE DISTRIBUTION

Among the total group of illnesses associated with the cases of poliomyelitis, there was a wide variation in the age of the individuals. No age group was conspicuous by its absence, but instead there were individuals ranging in age from a few weeks to over 70 years, whose illnesses were so closely linked to known cases of the disease as to indicate that in all probability they, too, were caused by the virus of poliomyelitis. When the age distribution curve of the 1,123 associated illnesses was plotted against that of the 1,074 reported cases of the disease, a close similarity was found. This is shown in Fig. 1, the data being presented in Table V. The age of highest incidence for both was from 5 to 9 years. The only significant difference noted was a slight increase in the proportion of associated illnesses in the 25- to 39-year age groups. This was found to be caused by the large number of parents of the younger and most susceptible age group, and probably indicates an unusually high degree of exposure among parents. The distribution of the various age groups in the general population is also shown for comparison. The similarity of the age-distribution curves of the two groups of illnesses, both of which occurred during the summer season, is interesting as confirmatory evidence of the poliomyelitic nature of the associated minor illnesses.

Since individuals of all ages are included in the group of contact illnesses, although *paralytic* poliomyelitis is particularly common in children, the ques-

tion arises as to whether age per se is related to the symptomatology resulting from infection with the virus. To answer this question, an age-distribution table of the individuals showing each symptom has been set up. The data are presented in Table VI. It will be seen that in the youngest age group,

TABLE V. AGE DISTRIBUTION OF POPULATION, POLIOMYELITIS CASES, AND MINOR ILLNESSES IN BUFFALO CITY AND ERIE COUNTY

AGE	POPULATION		REPORTED POLIOMYELITIS		MINOR ILLNESSES	
	THOUSANDS	PER CENT	NO. OF CASES	PER CENT	NUMBER	PER CENT
0-4	54.3	6.8	249	23.2	226	20.1
5-9	57.4	7.2	297	27.6	312	27.8
10-14	66.8	8.4	259	24.1	190	16.9
15-19	70.7	8.9	125	11.6	61	5.5
20-24	70.0	8.8	49	4.6	22	2.0
25-29	67.3	8.4	43	4.0	53	4.7
30-34	62.7	7.9	31	2.9	66	5.9
35-39	60.1	7.5	15	1.4	56	5.0
40-44	60.4	7.5	1	0.1	28	2.5
45-49	58.5	7.3	3	0.3	8	0.7
50-54	50.2	6.3	1	0.1	5	0.4
55-59	37.7	4.7	1	0.1	5	0.4
60-64	29.2	3.7			5	0.4
65-69	21.8	2.7			4	0.4
70-74	15.3	2.0			1	0.1
75-over	15.2	1.9				
Unknown					81	7.2
Totals	798.3	100	1,074	100	1,123	100

TABLE VI. AGE DISTRIBUTION OF THE INDIVIDUAL SYMPTOMS OF 1,123 CLOSE ASSOCIATES OF PATIENTS WITH POLIOMYELITIS*

AGE	FEVER (%)	NAUSEA VOMITING (%)	SORE THROAT (%)	HEADACHE (%)	"COLD" (%)	DIARRHEA (%)	SYMPTOMS SUSPICIOUS OF POLIO (%)	POLIO (%)
0-9	61.0	50.8	44.0	25.4	41.2	45.6	29.8	50.8
10-19	21.0	22.0	27.4	32.8	18.0	15.4	26.0	35.6
20-29	3.2	6.0	6.4	9.6	7.6	7.8	9.2	8.6
30-39	5.2	8.8	9.0	19.4	16.2	14.6	16.0	4.4
40-49	1.4	1.4	1.0	2.4	4.6	7.0	6.6	0.4
50-59	0.6	1.0	0.4	1.2	1.8	1.8	1.6	0.2
60-69	0.0	0.8	0.6	0.0	0.0	2.6	0.0	0.0
Unknown	7.6	9.2	11.2	9.2	10.6	5.2	10.8	0.0
Totals	100	100	100	100	100	100	100	100

*The boxed-in figures are those which are highest for the age group.

fever occurred in a particularly high percentage as compared with the other symptoms. Headache, on the other hand, was noticeably less common. These peculiarities of the younger age group are in no way indicative of a poliomyelitic infection, but are characteristic of the childhood type of reaction to any infection. It is interesting to note that headache and symptoms suggestive of the clinical disease were more common in the 10- to 39-year age groups, while diarrhea was somewhat more prevalent in the older age groups. The table also suggests that the clinical disease affected the 10- to 19-year-old group in the present epidemic out of proportion to other individual symptoms. This,

however, may possibly be a characteristic of the local epidemic. The results suggest that in attempts to detect the mildest forms of poliomyelitis, nausea, vomiting, and sore throat will be encountered at all ages in about the same proportion. However, fever is more characteristic of young children, diarrhea of the older age groups, while headache and symptoms suggestive of involvement of meninges and extremities are more common in the middle group or in young adults.

In view of the similarity of symptoms of the minor illnesses among the contacts to the early phase of the clinical disease, the problem of recognition of the one becomes essentially the same as early diagnosis of the other. Although it is to be hoped that methods for laboratory confirmation of the diagnosis will someday become available to all physicians, at present clinical observation and judgment remain as the only readily available means for diagnosing infections with the virus of poliomyelitis, mild, abortive, and severe, and, consequently, for planning a program for the control of epidemics. The present report has attempted to supply the practicing physician with a few additional aids in meeting his difficult diagnostic problems.

DISCUSSION

The cyclical epidemics of poliomyelitis are judged at the present time by the number of cases reported to departments of health. Yet a comparison of the proportions of paralytic and nonparalytic cases reported in different localities reveals a wide variation in the attitudes of physicians as to what constitutes a reportable case of the disease. In some localities, 99 per cent of the cases have evident paralysis; in others, only 17 per cent.[5] In some communities, cases which do not exhibit outspoken signs are ignored in order to allay public alarm; in others, physicians are on the lookout for early and mild symptoms regardless of the later course of the disease. Such differences in opinion are of more than academic interest, for they indicate the inadequacy of our present criteria for diagnosis and, because of this, allow no foundation on which to judge public health measures. It becomes essential, therefore, to obtain a clear picture of all the symptoms which may arise from an infection with the virus of poliomyelitis and not to confine attention to those cases presenting paralysis or even to patients showing changes in the spinal fluid.

From the data presented here and from numerous reports in the literature[2] there has come a body of evidence which leaves no room for doubt concerning the existence of mild cases of "abortive" poliomyelitis which are impossible to distinguish clinically from infections due to common bacterial pathogens. Usually they pass as unexplained fevers, attacks of nausea and vomiting, respiratory infections, or "grippe." Yet from such individuals the virus may be acquired by a sibling or friend who develops the paralytic form of the disease. The problem of preventing the spread of poliomyelitis, therefore, resolves itself in part into a widespread awareness of the mild forms which the disease may assume. Since there are no simple laboratory aids for confirming the diagnosis on a large scale as is possible with typhoid fever and

diphtheria, progress must be based on careful clinical observations at the present time.

How, then, is the clinical diagnosis of poliomyelitis to be made? Other central nervous system inflammations and, in particular, the various types of encephalitis may, of course, simulate the picture, and in the absence of an epidemic be difficult to differentiate. However, in individuals presenting meningeal and paralytic symptoms and showing the characteristic changes in the spinal fluid the diagnosis is immediately clear. Even in the absence of weakness or paralysis, signs of meningeal irritation with a spinal fluid showing a moderate increase in cells and protein may usually be considered diagnostic, especially in the presence of other cases in the community or following exposure to an epidemic area. Brainerd and associates[6] have pointed out that many cases show persistent spasm of certain groups of muscles with or without other symptoms, and that this is found in almost no other condition. A careful examination may detect mild grades of spasm, weakness, or incoordination which would be missed in a more cursory inspection. Especially in the presence of an epidemic, one may with fair confidence diagnose poliomyelitis whenever persistent muscle spasm, weakness, incoordination *or* change in the spinal fluid is noted in conjunction with an acute illness. It should be noted that numerous clinicians[7] have reported severe and even fatal poliomyelitis without changes in the spinal fluid.

The greatest problem naturally arises in diagnosing poliomyelitis in individuals who show only an acute illness without any of the signs pointing to the specific virus or central nervous system infection. In the absence of laboratory aids, help can be obtained from information of several types. (a) Experiences such as those presented in the body of this report suggest that the following symptoms either alone or in various combinations may result from infection with the virus of poliomyelitis: fever, nausea and vomiting, sore throat, nose cold, mild diarrhea, and headache. Whether still milder symptoms may also occur is not clear, but from epidemiological observations on nearly 1,000 families in which poliomyelitis has developed, we have gained the distinct impression that individuals with such "milder" symptoms or so-called healthy carriers are rarely, if ever, responsible for transmitting the disease. Casey[8] has come to a similar conclusion. From the viewpoint of public health, therefore, the main problem appears to center around the symptoms of an acute illness. (b) When the symptoms, mentioned in (a), result from agents other than the virus of poliomyelitis, the incubation period is shorter —almost always from one to three days. In contrast, the period between exposure and symptoms in poliomyelitis is usually from one to two weeks, and occasionally longer. A history of contact with an illness having a latent interval of from one to three weeks reinforces the suspicion that the illness in question may be mild poliomyelitis. (c) Since it has been estimated by various workers[9] that during an epidemic period there are from six to twenty illnesses of a mild nature caused by the virus for every individual diagnosed as having the disease, the presence of paralytic cases in a family or community should

attract attention to the minor sicknesses and arouse suspicions concerning the etiologic nature. (d) Finally, poliomyelitic infections are relatively more common in warm weather than in cold, a fact which is opposite from the seasonal periodicity of other common infections. While it is impossible to establish the diagnosis in mild illnesses without laboratory confirmation, these four guides offer a helpful basis for judgment.

If physicians are to make the diagnosis of poliomyelitis on all individuals whose symptoms give rise to suspicions as already discussed, an entirely new problem presents itself to our public health agencies whose function it is to prevent or control epidemics of all kinds. Should physicians be urged to report poliomyelitis whenever suspicions are aroused, even though no means exist for confirmation? Or should minor illnesses of uncertain nature be ignored? Three alternatives are open. The first, which is now in vogue in most states, is to tabulate the statistics of an epidemic for general purposes only, but to carry out no definite program of control. This stand has been based on the futility of experiences which have attempted to check the spread of the disease by quarantine of the reported cases. In the light of present-day knowledge such quarantine could have little, if any, value. The second alternative would be to insist on the reporting and isolation of all suspicious illnesses. Since the disease appears to be spread largely through contact with individuals who have active symptoms, theoretically, at least, rigid quarantine should be effective. In practice such a policy has proved impossible to carry out, both because of the disinclination of physicians to report the diagnosis on insecure evidence and the futility of measures in such attempted drastic and widespread quarantine. A third alternative would be to encourage physicians to report even the mildly suspicious illnesses but to depend on public education for control. Certain facts concerning the methods of spread are known, which could be brought to the attention of families, neighborhoods, and communities during an epidemic, and should enable them to carry out any local measures which, in conjunction with local health officials, would be deemed advisable. This last procedure would appear to be more practical and probably more effective also than either of the foregoing. It would place the responsibility and initiative with small local groups rather than with the unsatisfactory police power of a health department.

SUMMARY AND CONCLUSIONS

Illnesses of 1,123 close contacts of patients with poliomyelitis have been studied.

The most common symptoms of the group were fever, nausea and vomiting, sore throat, and a "cold." Headache, symptoms referable to the central nervous system, and diarrhea were encountered less frequently. Combinations of one or more were usually found.

The similarity of these symptoms to those occurring in the preparalytic state or in the nonparalytic form of clinical poliomyelitis was pointed out.

All ages were affected, the oldest being 74 years, the youngest 6 weeks. The age distribution was similar to that of the reported cases of poliomyelitis occurring during the same season.

When the various symptoms were reviewed in respect to the age of the individuals concerned, it was noted that fever was particularly common in children below the age of 10 years, headache among the 10- to 40-year group, and diarrhea in the older individuals. Nausea, vomiting, and sore throat affected the various age groups in approximately the same proportion.

Although no laboratory aids are readily available to verify clinical diagnoses of poliomyelitis infections, the following circumstances assist in reaching a conclusion: (a) a similarity of the symptoms to those known to occur in mild illnesses caused by the virus; (b) evidence of an incubation period of from one to three weeks; (c) the presence of known cases of poliomyelitis in the neighborhood; (d) occurrence during the season of warm weather.

It is suggested that if the mild as well as the severe cases of infection with the poliomyelitis virus were reported to departments of health, a more adequate program for public education and control of the disease could be evolved.

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THE EFFECTS OF ACTIVE IMMUNIZATION OF THE MOTHER UPON THE OFFSPRING

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THE human placenta is of the hemochorionic type characterized by the intimate relation of the fetal capillaries and the maternal circulation.[1] The trophoblast is the parenchyma and unit of the placenta, constituting the essential tissue which sustains the growth and nutrition of the embryo by securing nutriment from the maternal organism.[2] The endothelium of the bulging fetal capillaries is closely applied to a thinned-out sheet of syncytial trophoblast, a structural mechanism admirably adapted for active and direct exchange of gases and metabolites between the intervillous space and the fetal circulation. This relationship bears comparison with the cytological features of the pulmonary alveoli and the kidney glomeruli.[3] The trophoblast, clothing the chorionic villi, is also the barrier between mother and fetus, for the syncytium has selective and phagocytic properties which regulate the exchange between mother and fetus, and fetus and mother.

To all intents and purposes, the hemochorionic placenta is composed of myriads of semipermeable membranes, obeying the physicochemical laws of such membranes. The size of the molecule largely determines what traverses and what fails to pass the placental barrier, which, as has been noted, has the capacity of halting the passage of foreign material.[4] So we observe the free passage and equal distribution of chemical substances and soluble drugs between maternal and fetal circulations.[4, 5] The same principles and findings hold true for antibodies, for it has long been recognized that antitoxins, such as diphtheria, tetanus, and scarlet fever, are approximately equal in the blood of mothers and newborn babies.[6] Similarly, isohemolysins, isoagglutinins,[4, 5, 8] and other agglutinins[9] and hormones[5] may readily traverse the placenta. The antibodies against poliomyelitis,[10] influenza, lymphogranuloma venereum,[12] and other virus diseases[5, 13] have been transmitted from mother to fetus. Antistreptolysin,[14] staphylococcus antitoxin,[15] and antipneumococcic antibodies[16] also readily gain entrance into the fetal circulation if the mother possesses such antibodies. The present concept of the pathogenesis of erythroblastosis fetalis is based upon the transmission of isohemolysins from mother to fetus.[8]

It is worthy of emphasis that the uninjured chorion is relatively impervious to colloidal and particulate matter. Maternal antibodies, however, if present, readily pass the placental filter, but toxins meet resistance, and foreign proteins are normally phagocytosed by chorionic cells, the protective barrier of the fetus against bacteria and viruses.[5, 13] Failure of this action may, on occasions, lead

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to the death of the fetus, to intrauterine disease or malformations manifesting themselves in the baby at birth or some time thereafter, or to processes of sensitization with various allergic expressions.[13, 17]

This evidence logically leads to the conclusion that the immune properties of the newborn depend upon the immunologic status of the mother. It is as rational to remedy maternal immunologic deficiencies as to correct maternal lack of protein, minerals, vitamins, anemia, or any other deficiency which may be deleterious to the welfare of the unborn baby. Appropriate studies should be undertaken during pregnancy to reveal remediable deficiencies, including immunologic ones, which are pertinent to the resistance of the offspring.

TABLE I. RESULTS OF SCHICK TESTS AT DIFFERENT AGES (1914-1923)*

AGE	PER CENT SCHICK POSITIVE	PER CENT SCHICK NEGATIVE
Newborn	16	84
0- 3 months	28	72
3- 5 months	43	57
6- 7 months	57	43
7- 8 months	63	37
8- 9 months	84	16
9-10 months	93	7
10-11 months	87	13
11-12 months	91	9
1- 3 years	83	17
4- 6 years	61	39
6- 7 years	50	50
7- 8 years	44	56
8- 9 years	37	63
9-10 years	32	68
10-11 years	29	71
11-12 years	28	72
12-13 years	24	76
13-14 years	23	77
14-15 years	20	80
15-16 years	18	82
16-17 years	18	82
Over 17 years	14	86

*B. Schick in *Brennemann's Practice of Pediatrics.*

Diphtheria and pertussis are the two most important preventable contagious diseases of infancy. There has been a subtle change in diphtheria susceptibility in the past generation, a change not properly evaluated. Whereas twenty to thirty years ago 80 to 90 per cent of adults were proved immune to diphtheria,[18] in recent years only about 50 per cent of adults have been shown to be immune.[19, 20] By means of Schick tests and titration of circulating antitoxin, abundant testimony has been collected by different investigators in diverse localities to establish the changed immunologic status of the adult population to diphtheria.[19, 20, 21, 22]

Analysis of the data, compiled by Schick largely from statistics in Vienna and from New York, revealed that in the period from 1914 to 1923, 86 per cent of adults were immune to diphtheria, as were the newborn babies of that generation. The era of prophylactic immunization then began with interesting and significant changes. It gradually came to light that the passage of years produced a waning of artificially induced immunity (Table II). After three

TABLE II. DURATION OF DIPHTHERIA IMMUNITY*

INTERVAL AFTER IMMUNITY	SCHICK POSITIVE (%)	SCHICK NEGATIVE (%)
6 mo.	0.4	99.6
1 yr.	3	97
3 yr.	8	92
5 yr.	34	66

*From Brandon and Fraser, Studies of ninety-four children Schick negative after three toxoid injections at three-week intervals.

years, when only 8 per cent of successfully immunized children became Schick positive, the percentage increased precipitously so that at the end of five years, between 25 and 35 per cent of the immunized groups became Schick positive.[23, 24] This finding has given rise to the approved practice of a booster reinjection of diphtheria toxoid (and other antigens) at intervals of three years. Since this practice is far from universal after 6 years of age, the adult has suffered further loss of immunity (Table III). Schick tests, confirmed on occasion by blood antitoxin titrations, have demonstrated that from 30 to 87 per cent of adults in different regions are susceptible to diphtheria. Investigations in our clinic on young, pregnant women, nearly all of whom had been immunized in early childhood and were Schick negative on entering school, substantiate the recent statistics that about 50 per cent of adults are no longer immune to diphtheria. Obviously this increased susceptibility must necessarily be reflected in corresponding lack of immunity in the newborn babies, since such immunity is passively transferred. Recent data and our own studies of diphtheria immunity in mother and offspring support this contention.[20, 21] (Table IV.)

TABLE III. DURATION OF SCHICK IMMUNITY

DATE	AUTHOR	NO. TESTED	IMMUNITY STATUS	SCHICK POSITIVE (%)
1936	Fraser and Brandon[24a]	94	5 yr.	34
1938	Schwartz and Janney[24b]	145	6 yr.	22
1941	Lewis, J. T.[22]	51	51 to 53 mo.	37
1943	Duke and Stott[24c]	164	5 yr.	25

TABLE IV. DIPHTHERIA IMMUNITY IN ADULTS (1932-1944)

AUTHORS	DATE	REGION	NUMBER	AGE GROUP	SCHICK POSITIVE (%)
Cooke and Sharma[19a]	1932	St. Louis	643	30 years	30
Liebling and associates[21]	1941	Chicago	—	25 years	52.8
Campbell[19b]	1941	Halifax	405	20 years	59
	1941	Halifax	243	18 years	80
	1941	Halifax	250	25 years	55
	1941	Halifax	—	22 years	71
	1941	Halifax	558	Adult	87
Wishart[20c]	1943	Canada	74	20 years	52.7
Karelitz and Moloshok[20b]	1944	Americans in Africa	1,283	20-25 years	28.6
Wright and Clark[20a]	1944	London	250	28 years	51.6
	1944	London	62	31 years	58
Bull. U. S. Army[23b]	1944	U. S.	2,933	20-30 years	44
Cohen and associates	1946	New York City	175	Pregnant women	52

The reason for the waning immunity of the adult against diphtheria has been ascribed to the present lack of contact with the diphtheria bacillus, a sequel of prophylactic immunization, and the decline of diphtheria. So infrequently do adults today come in contact with the toxogenic bacilli that the circulating antitoxin often falls below the critical titer for a negative Schick test.[22, 25] The persistence of artificial immunity depends upon periodic artificial restimulation or continuation of the immune response by exposure to the diphtheria environment. Epidemiologists, aware of recently increasing diphtheria outbreaks, have come to the conclusion that the diphtheria problem of the future is concerned with older children and adults, for they have borne the brunt of recent diphtheria epidemics.[23, 25]

TABLE V. STAPHYLOCOCCUS ANTITOXIN CONTENT—UNITS PER CUBIC CENTIMETER*

MATERNAL	FETAL	INFANTILE	AGE OF INFANT
122	248	72	4 weeks
70	86	94	4 weeks
58	57	10	4 weeks
51	77	23	4 weeks
48	190	38	4 weeks
91	93	29	8 weeks
–	80	20	8 weeks
11	22	3	8 weeks
23	41	7	8 weeks
93	100	10	8 weeks

*Bryce and Burnet.[15a] Illustrates passage of staphylococcus antibodies from mother to baby; decrease in the older infants.

While the Schick test is not an exact measurement of antitoxin content, it has an exceptionally good correlation with immunity against diphtheria.[22] Since the skin of a newborn baby is not fully reactive, immunity in the baby can be better evaluated by performing Schick tests on the mother.[20, 21] This practice is not only accurate but obviates the time-consuming antitoxin titrations which yield no practical advantage over the Schick tests.[20, 21, 22] If a pregnant mother is Schick positive, she should be injected with diphtheria toxoid to increase her immunity to a level (the Schick negative state) which is certain to confer adequate immunity upon the baby.

Active immunization of the pregnant woman against diphtheria has already been performed with gratifying results. Mothers formerly Schick positive, with low blood diphtheria antitoxin content, were converted by active immunization during the latter part of pregnancy to immunity against diphtheria.[21] It should be remembered that the Schick test itself, by virtue of the injected toxin, is not only a measure of antitoxin content, but may be a stimulating antigen, and an effective boosting agent in those who have previously been inoculated with toxoid or stimulated by exposure to carriers.

Just as the easily performed Schick test and the precision of antitoxin determinations have yielded abundant data about diphtheria immunity, so has the absence of such tests accounted for the paucity of authentic data about pertussis immunity in the adult and the infant. It was only five years ago that relatively accurate data was collected, which pointed to the fact that only 15 to 30 per cent of adults have protective antibodies against pertussis.[26] Similar

studies of a small series of newborn infants suggested that about 15 per cent have some degree of immunity against whooping cough.[27] This low percentage of infantile protection receives clinical confirmation from the frequent incidence of pertussis in the infant,[28] when it is attended by the highest mortality. A ten-year survey of whooping cough at Willard Parker Hospital revealed that 5 to 6 per cent of its incidence occurs in the first six months of life.

Lack of immunity in the mother results in susceptibility to pertussis of the infant. It occurred to one of us (P. C.) that it was not only desirable but feasible to protect the infant against pertussis by inoculating the mother during pregnancy with a potent pertussis vaccine. It had been amply demonstrated that immunity can be produced by such vaccination.[30] Because of the evidence detailed at the outset, we believed that antibodies so produced would be transmitted through the placenta to the baby. Accordingly, 170 women were injected at two-week intervals from the sixth to the eighth month of pregnancy in doses totaling from 90 to 150 billion of pertussis vaccine. Immunologic studies of thirty women of this group demonstrated that all developed high titers of immune bodies following such vaccination, and that these antibodies were regularly transmitted to their babies in a titer quantitatively of the same order. Similar studies repeated at intervals of five and one-half to ten months in a group of ten mothers and babies (Table VI) showed that active immunization of the

TABLE VI. RETESTS OF VACCINATED MOTHERS AND THEIR BABIES*

SERIAL	NAME	BLED	PERIOD	RESULT			
				AGGLUTINATION	C. F.	MOUSE PROTECT SURV.	MOUSE PROTECT PER CENT
C2	Mrs. D. B.	3/18/42	9 mo. after vaccination	800	0.02	2/8	25
	Baby D. B.	3/18/42	8½ mo. old	0	0	N.T.†	
C3	Mrs. P. B.	2/26/42	8 mo. after vaccination	10	0.02	0/10	0
	Baby P. B.	2/26/42	6½ mo. old	0	0	0/10	0
C5	Mrs. M. E.	4/28/42	10 mo. after vaccination	75	N.T.	8/10	80
	Baby M. E.	4/28/42	8½ mo. old	0	N.T.	0/4	0
C6	Mrs. G.	2/19/42	8½ mo. after vaccination	?‡	N.T.	N.T.	
	Baby G.	2/19/42	7 mo. old	?	0	N.T.	
C12	Mrs. A. M.	3/18/42	8½ mo. after vaccination	600	0	5/10	50
	1st Twin P. M.	3/18/42	8½ mo. old	slide 0	0	1/6	0
	2nd Twin S. M.	3/18/42	8½ mo. old	slide 0	0	N.T.	
C15	Mrs. T.	2/26/42	8½ mo. after vaccination	150	0.02	6/10	60
	Baby T.	2/26/42	8 mo. old	0	0.02	0/10	0
C20	Mrs. S. K.	4/28/42	9½ mo. after vaccination	25	N.T.	6/10	60
	Baby H. K.	4/28/42	8½ mo. old	0	N.T.	0/10	0
C25	Mrs. E. A.	4/12/42	9 mo. after vaccination	400	N.T.	9/10	90
	Baby E. A.	4/12/42	8 mo. old	0	N.T.	0/9	0
C36	Mrs. H. L.	3/12/42	7½ mo. after vaccination	0	0.02‡	3/10	30
C39	Mrs. M. V.	3/12/42	8 mo. after vaccination	600	0.02	4/10	40
	Baby M. V.	3/12/42	5½ mo. old	0	0	N.T.	

*Illustrates retention of antibodies in mothers actively immunized and loss by babies passively immunized.

†Not tested.

‡Strongly hemolyzed.

mother resulted in the persistence of antibodies, while it may be assumed that the babies retained little or none of their antibodies, passively obtained. Larger doses of the vaccine may yield a more lasting immunity for the baby, a hypothesis we shall test.

The follow-up studies regarding the incidence of pertussis in 100 babies of immunized mothers were compared with an equal number of babies of unimmunized mothers. In the latter group, in the first six months of infancy, there were six exposures resulting in three cases of whooping cough. During the same age period of the immunized group there were eight exposures, three due to close contact, but no cases of whooping cough developed. In the second six months of life each group yielded two cases of whooping cough. Since our studies had revealed that the immunity of the babies unlike the mothers, does not persist after 5 to 6 months of age, the occurrence of pertussis in our immunized group in the second six months of life occasioned no surprise. While our data and numbers are too meager and too incomplete to lead to conclusions, the results of the incidence of whooping cough, within limits, are in keeping with the expectancy of passive immunization.

Three groups of investigators using different immunologic techniques have obtained results which led to the conclusion that pertussis antibodies are transmitted by the placental route to the newborn baby.[31] One group, employing the opsonocytophagic method, presented evidence that pertussis vaccination during pregnancy increases the opsonophagocytic powers of the mothers which were quantitatively transmitted to their babies. No further studies of the persistence of the increased opsonophagocytosis, nor a clinical follow-up of the babies prenatally immunized, were reported.

The timing of the injections is of the utmost importance. We administered our vaccine during the last third of pregnancy, because during that period both placental and fetal circulations are amply developed for the proper circulation and filtration of the diffusible antibodies.[2, 4, 32] We aimed to complete our prophylaxis six weeks before term, for both pertussis and diphtheria immunization yields its peak of immune titers four to eight weeks after the termination of adequate prophylaxis.[21, 33] By such timing, we planned to have the mother reach the pinnacle of immunization at term so that the baby could be endowed at birth with the highest antibody content. Our data support the success of our timing and termination of our prophylaxis.

Passive immunity of the baby induced by active immunization of the mother is the best available method for producing immunity in the young infant. Studies, just after birth, of the electrophoretic pattern of the serum proteins of mothers and their babies lend support to this opinion.[34] Immunity has been demonstrated to reside in the gamma globulin fraction, and it is precisely in this and only in this antibody fraction that the baby equals or even surpasses its mother's component. This finding is consistent with the maternally conferred immunity of the newborn. It is well known among immunologists that the newborn and very young infant is a poor anitbody producer.[35] Attempts at active immunization during this early age period have yielded little or no demonstrable results.[36]

When multiple antigens are simultaneously injected, the antibodies called into production are quantitatively in ratio to the potency of the antigens.[37] Diphtheria toxoid is a very potent antigen, as is the pertussis vaccine (to a lesser degree), but the Rh factor is a relatively weak antigen. It is sound theory and a hopeful practice to administer combined diphtheria pertussis vaccine early in pregnancy, for by so doing, the production of anti-Rh antibodies may be suppressed. This method of counterimmunization has already been attempted in women with a history or background of Rh sensitization, but data are insufficient to lead to definite conclusion.[37] This procedure, nevertheless, is an added attraction and argument for active immunization during pregnancy for the benefit of the offspring, but it is important to note that the inoculations begin during the first trimester instead of the last trimester of pregnancy.

From our observations we can definitely state that active maternal immunization has no observable deleterious effects upon the offspring. The mother, however, may often suffer local discomfort for a brief period, and at times fever and systemic reactions develop, but these reactions have no ill effects upon the pregnancy. An intradermal test with a one to ten dilution of diphtheria toxoid is first performed on all Schick positive cases (Moloney test). If this reaction is definitely positive within one-half hour, either diphtheria toxoid is omitted if the reaction is very marked, and plain pertussis vaccine given, or the initial dose of 0.1 c.c. diphtheria toxoid is followed by 0.25 c.c., 0.5 c.c., and 1 c.c. added to the pertussis vaccine in the same syringe. We favor the use of a fluid diphtheria toxoid combined with a pertussis vaccine containing 15 billion bacilli per c.c. beginning with 1 c.c., followed with 2 c.c. for two doses twice, and then 3 c.c., totaling 120 billion pertussis bacilli. In sensitive cases the diphtheria toxoid in increased dosage is added to pertussis vaccine as described. This method causes fewer and less reactions than the alum preparations which, in addition to producing greater reactions, often leave annoying and embarrassing nodules of which the women complain, and because of which they may object to the continuation of immunization.

Our present program is to take inventory of the immunologic status of the pregnant woman at the earliest opportunity. Deficiencies in immunity against diphtheria, pertussis, or any remediable infection which may be endemic such as influenza, streptococcus infections, may then be corrected by appropriate combined immunization of the mother in the latter part of pregnancy. The maternal immunity so induced, as has been frequently demonstrated, will be transmitted to the infant to endure for the first few months of life. At the age of 6 months, appropriate active immunization should be administered to the infant. Our scheme of active combined maternal immunization is not unlike the prophylactic, combined immunizations which the Armed Services rendered its members during World War II with such effective and gratifying results.[38]

SUMMARY AND CONCLUSIONS

1. The human placenta readily transmits diffusible substances such as antitoxins and antibodies.

2. Lack of immunity in the mother is reflected in a corresponding lack of immunity of her baby.

3. Apparently as a result of childhood prophylaxis, women today lack immunity to diphtheria in about 50 per cent of cases in contrast to 85 per cent immunity in the preimmunization era of the past generation.

4. About 80 per cent of women and about 85 per cent of babies are not immune to whooping cough as demonstrated by lack of protective antibodies.

5. Since the young infant does not produce a proper titer of antibodies by active immunization, it should be protected during the perilous first few months of life by passive immunization.

6. Active immunization of the mother in the last of trimester of pregnancy will confer passive immunity upon the offspring for the first few months of his life against diphtheria, whooping cough, and probably against other diseases for which we have effective vaccines.

7. Vaccine and toxoid therapy during pregnancy may serve to suppress formation of anti-Rh antibodies. This method of counterimmunization is an additional argument for active immunization in pregnancy, but for this purpose the inoculations should be given from the first trimester of pregnancy through the last.

8. Local reactions occur frequently, but systemic effects are infrequent.

9. The procedure of active immunization during pregnancy is harmless, for we have observed no ill effects upon the babies or upon the mothers during the course of pregnancy.

10. A program is presented of combined, active, maternal immunization remedying immunologic deficiencies of the mother to the immunologic advantage of the offspring.

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AN EPIDEMIC OF DIARRHEA IN THE NEWBORN NURSERY CAUSED BY A MILK-BORNE EPIDEMIC IN THE COMMUNITY

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IN AN epidemic of diarrhea in the newborn nursery, too often the first thought is to close the obstetric floor. It is the purpose of this article to present a nursery epidemic which was secondary to a milk-borne epidemic of diarrhea in the community. From the results it would seem advisable to consider that a disease in the community may be the possible source of a nursery infection.

On Oct. 1, 1945, Dr. M. O. Steffen, at Great Bend, Kan., reported to the Kansas State Board of Health some deaths of infants in the newborn nursery at St. Rose Hospital. A preliminary investigation revealed that there had been occurrences and recurrences of diarrhea in the nursery and in infants dismissed from the nursery since June. It was also determined that there had been several cases of diarrhea in the community and neighboring communities for several months. Because of the possibility of a common source for this diarrhea, a more detailed study was conducted.

There were twenty-four infants who had either developed this disease in the hospital nursery or had developed it after leaving the nursery and then had returned to the hospital. Of these twenty-four infants, nine died. During this period of time there had been 278 births in the hospital. This paper deals with these twenty-four cases, referring to the community study only where it has a bearing on the hospital study.

Fifteen infants developed symptoms in the nursery, while nine had been discharged from the hospital and returned. Of these nine infants, seven had the history of contact with a case of gastroenteritis at home; one (Case 11) returned to the pediatric ward because of a feeding difficulty, and seven days after admission, developed diarrhea simultaneously with the development of several cases in the nursery. The ninth infant (Case 23) developed symptoms the very day he left the hospital, so we can conclude that he contracted the disease there. The mother of one patient (Case 19) developed gastroenteritis in the hospital, although the infant did not develop the disease until two days after discharge. In Case 18 the histories given by the family varied. One gave the first day after discharge from the hospital as the day of onset; the other gave the fifth day. On the second day after discharge, a member of the household developed diarrhea and subsequently two other members, before the infant returned to the hospital on the eighth day. All three cases (Cases 18, 19, and 23) were recorded on Chart 2. A total of nineteen probably contracted the disease in the hospital. It can be seen from Chart 1 that several infants developed symptoms shortly after leaving the hospital, so it is possible that they contracted the disease there or at home.

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Diarrhea was the first, and often the only symptom, which might vary from a few soft frequent stools to extremely watery ones. The next most common symptom was vomiting, then dehydration, cyanosis, collapse, pain, and fever, in that order. In three infants who died, early and extreme setting of the muscles in rigor mortis occurred. In many of these cases, the diarrhea seemed to be recurrent over periods of time as long as six weeks, just as it was in some of the adult cases. The incubation period of the disease varies from one to seven days, most commonly six. In only one case was the onset less than 4 days after birth; the onset in this case was 3 days. The average age at death was 25¼ days; the range was 11 to 54 days. The average number of days between onset and death was 16½ days; the range was 4 to 38.

It seems logical to divide this study into three parts: epidemiological, milk sanitation, and bacteriologic.

EPIDEMIOLOGICAL

The science of epidemiology is older than the science of bacteriology; in fact, at least one classical epidemiological study was made before the advent of bacteriology. The epidemic study in this case should be based upon the knowledge of the method of spread of gastrointestinal diseases rather than upon the specific organism.

From the Charts 1 and 2, these points can be noted:

1. There were six outbreaks in the nursery, with the development of from one to six cases in each outbreak.

2. These outbreaks were separated by periods of 15, 7, 49, 31, and 10 days. It would seem impossible for the infection to have been maintained by passage from infant to infant or through fomites; it must have been reintroduced.

3. There were no secondary cases occurring in the nursery, with the possible exception of the August outbreak.

4. Prior to every outbreak in the nursery, except the one in August, one mother or nurse on the obstetric floor developed the disease. In the August and October outbreaks, mothers had had the disease shortly before entering the hospital. In August, the second case (Case 15) appears to be secondary to Case 14, the infant of one of these mothers.

5. In every case where the mother had had the disease, her infant developed it.

6. One case (Case 11) occurred in the pediatric ward (farthest removed from the nursery) simultaneously with the late June outbreak in the nursery.

7. One mother (Case 16), who did not have diarrhea, came from a family in which two children did.

In addition to the information shown on the chart, several cases of gastroenteritis developed in other parts of the hospital, in medical and surgical patients, and in twenty-four nurses and nuns.

The hospital nursery had been very crowded, of necessity housing three times the number of infants it was built to accommodate. A proportionately large number of premature infants was in the nursery. A shortage of profes-

sional personnel existed. Such conditions resulted in some breaks in technique, but they were not gross breaks and they would not explain the epidemic.

But the nursery outbreaks can easily be explained on the basis of secondary infection from infected mothers or nurses if we keep in mind a well-known fact in the epidemiology of gastrointestinal diseases, namely, that apparently healthy persons who have ingested organisms are carriers of those organisms until they are eliminated from the alimentary canal. These organisms may be eliminated in one or two days. Nevetheless, until they are eliminated, persons harboring them are temporary carriers, capable of passing the infection on to others. The only condition which would result in a large group of temporary carriers is a recent ingestion of a contaminated food or water.

Since one mother or nurse, or both, developed the disease prior to every outbreak, it shows that there was repeated ingestion of contaminated food or water and that there was an opportunity for others, who were not sick, to become temporary carriers. This is demonstrated in the case of the infant (Case 16) whose mother, apparently well, came from a family where other members had diarrhea when the mother was admitted to the hospital.

Each infant infected in the hospital was secondarily infected from his mother or from a nurse who had received the infection from contaminated food or water. Likewise, each individual infected at home was secondarily infected by a member of the family who had, in most instances, not eaten food at the hospital.

In addition, there were several hundred cases of diarrhea occurring in the community (histories were obtained on more than 400 which occurred between July 1 and October 15) and several cases occurred in outlying communities. The hospital, the city, and the outlying communities had separate water supplies.

The only foods common to the hospital and city which were not cooked before use in the hospital were bread, lettuce, cold meats, and milk. The only persons who developed diarrhea in the outlying communities were persons who had been using milk from the dairy at Great Bend, which supplied the hospital. Only twenty-one of the twenty-four mothers could be contacted, but the one food that all twenty-one used at the hospital was milk. Two of these mothers developed diarrhea before entering the hospital, but they bought milk from the same dairy.

From an epidemiological standpoint, a contaminated milk supply, which had not been adequately cleaned up over a long period of time, was a source of the infection. It could account for the epidemic in Great Bend, the cases in the outlying communities, the cases among patients in the hospital, among nurses and nuns (many of whom had not eaten food away from the hospital for months), and for the outbreaks among the infants in the hospital. All of these cases cannot be explained in any other way.

MILK SANITATION

Milk for 90 per cent of the community came from two dairies which supposedly sold pasteurized milk. Inspection revealed both to be filthy, filled

with flies, to have dogs in the milk room, to lack handwashing facilities, to have dust blowing in, to have no recording thermometers on the pasteurizing vats, and in one dairy a rag had been tied over a leak in a water pipe directly over the cooling coils. From this rag, water dripped into the pasteurized milk. The cleaning and sterilizing of bottles was so carelessly done that in the exchange of bottles, an infection in one dairy could easily spread to the other. A heavy collection of milkstone on the pipes testified to the fact that they had not been properly cleaned for months.

The phosphatase tests on milk from both dairies showed that the milk had not been pasteurized. Bacterial counts on the milk from both dairies were over three million per cubic centimeter. Further bacterial studies on the milk will be included under the next heading.

BACTERIOLOGIC

The bacteriologic study of the cause of illness and death of infants in the St. Rose Hospital, Great Bend, was started on Oct. 1, 1945. A complete laboratory was set up in the hospital and three bacteriologists from the State Public Health Laboratories were assigned to study this epidemic. Stool specimens were obtained from all sick and some normal infants; from hospital nurses and employees; from mothers, and from residents of Great Bend who were sick or had recently been sick. Rectal swabs were used to collect the specimens except in cases of the infants. The stools were plated directly on SS agar, MacConkey's agar, and desoxycholate agar. Tetrathionate broth and Selenite F broth were used as enrichment media. All suspicious colonies were removed and placed in Kligler iron agar. These cultures were then sent to the Central Public Health Laboratories, Topeka, where complete study and identification was made.

Because of the clinical symptoms of the disease in some infants, and the history of a sick father who returned by airplane from overseas, efforts were made to isolate all types of organisms, even *Vibrio comma*. Although *Pseudomonas aeruginosa* was isolated from the first case seen on October 1, it was difficult to believe this was the etiological agent, therefore, every effort was used to eliminate all other possible organisms. Streptococci, both aerobic and anaerobic, were looked for in addition to the afore-mentioned groups of organisms. More than 500 stool specimens were examined.

A brief summary of the findings on stool specimens is given in Table I.

In addition to the results already given, a large number of Proteus and Salmonella-like cultures, which are, for the present, being classified in the paracolon group, were isolated. More than 700 cultures were studied. The identification consisted of cultural, biochemical, and typing for antigenic characteristics.

It is interesting to note that nurses in the nursery and pediatric departments were carriers of *Ps. aeruginosa*. Another finding of interest was the isolation of *E. typhosa* from one of the nurses.

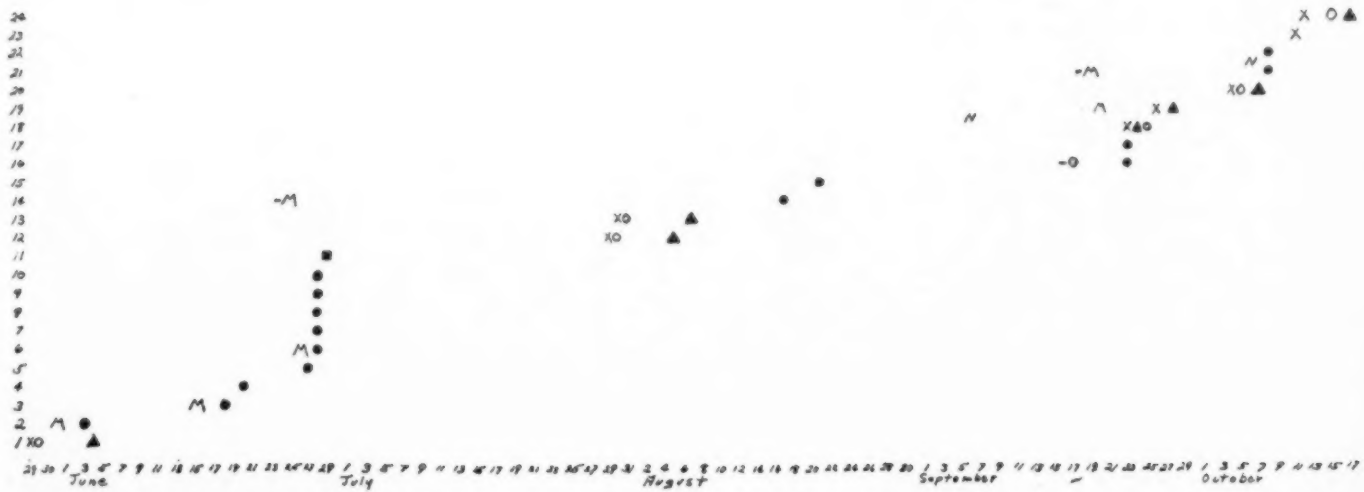

Chart 1.—Showing place and time of onset of symptoms and probable source of infection. The solid figures represent onsets which were on the dates corresponding to the vertical lines.

● Onset in the nursery.

■ Onset in pediatrics.

▲ Onset at home.

X Represents date of dismissal from hospital of those who were dismissed and then returned.

The letters represent the date of onset in cases which were probable sources of infection for the infants except in cases of other family members where this represents the date the infant came in contact with them.

M Mothers who developed diarrhea in the hospital.

-M Mothers who developed diarrhea before entering.

N Nurses on the obstetric floor who developed diarrhea.

O Other members of the family with diarrhea when infant returned home.

-O Other members of the family who had diarrhea at the time the mother entered the hospital.

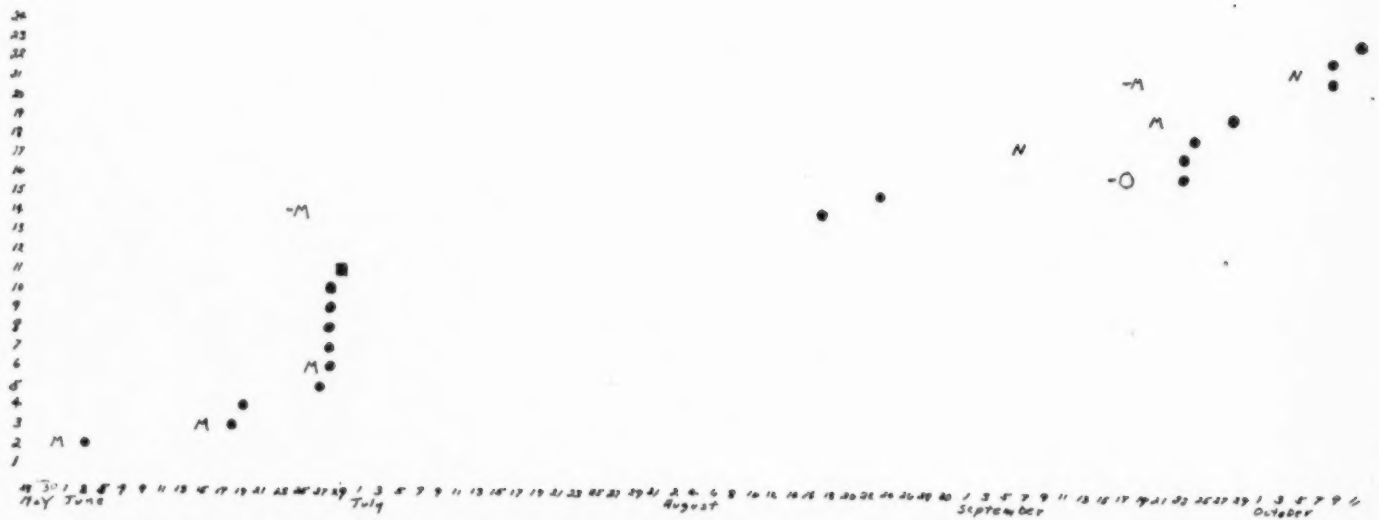

Chart 2.—Patients who contracted the disease from a source in the hospital.
■ Onset with probable source in pediatrics.
● Onset with probable source in the nursery.
No figure is shown for dismissal from the hospital. Otherwise the legend is the same as in Chart 1.

TABLE I

A. Number of infants (under 2 years of age) studied bacteriologically	38
Ps. aeruginosa isolated	24
B. Number of infants followed clinically in this study	24
Number above infants studied bacteriologically	9
Ps. aeruginosa isolated	9
C. Number normal infants studied bacteriologically	13
Ps. aeruginosa isolated*	5
D. Autopsies on infants	2
Ps. aeruginosa isolated (liver, spleen, gall bladder, intestines)	2
E. Rectal swabs on nurses and employees in hospital	103
Ps. aeruginosa isolated	16
Eberthella typhosa isolated	1
Shigella alkalescens isolated	2

*Four of the 5 infants became sick later. The mother of the fifth infant developed diarrhea at the time of dismissal from the hospital. Due to discontinuance of public health nursing services, this infant could not be followed.

Water Supply.—There were three different sources of water for the community: hospital, city, and private wells. The hospital had its own water supply and bacteriologic examinations showed the water to be free of coliform organisms and *Ps. aeruginosa.*

The city water supply (17 samples) did not show the presence of coliform or *Ps. aeruginosa.* It is chlorinated continuously and tested regularly under the supervision of the State Board of Health. It is estimated that there are some, 1,300 private water supplies in Great Bend. Upon inspection by the sanitary engineers, none was found cross connected to the city water. Seventy-two samples of water from private wells were examined and coliform organisms found in sixteen of them. *Ps. aeruginosa* was isolated from four wells.

Milk Supply.—The milk sanitarians collected many samples, raw and pasteurized, at the plants and at the time of delivery, and brought them to the laboratory for examination. The bacteriologic examinations consisted of the standard plate count, microscopic examination, coliform determinations, and phosphatase tests. A summary of the results is given in Tables II and III.

TABLE II

DAIRIES	NUMBER	PER CENT OF TOTAL VOLUME OF MILK
Pasteurized	3	80.5
Raw	6	19.5

TABLE III

	STANDARD PLATE COUNT			COLIFORM		PHOSPHATASE TEST			
MILK SPECIMENS	NO. OVER 10,000	NO. OVER 100,000	NO. OVER 3,000,000	NO. TESTED	NO. +	NO. TESTED	NO. +	NO. ±	NO. −
Pasteurized	38	28	8	30	23	64	9	14	41
Raw	19	14	2						

The bacteriologic analysis of the milk showed that more than 22 per cent of the samples of Pasteurized Milk No. 1 had a standard plate count of over 3,000,000. Pasteurized Milk No. 2 had an average standard plate count of 110,000, and Pasteurized Milk No. 3 an average of 95,000.

The phosphatase tests showed that 7 per cent of the samples of Pasteurized Milk No. 1 was insufficiently pasteurized; 23 per cent of the samples of Pasteurized Milk No. 2 was not sufficiently pasteurized.

Ps. aeruginosa was isolated from the water running from the dirty rag which hung over the cooler into the milk.

TREATMENT

The treatment, before isolation of the organism, had consisted of penicillin, transfusions, parenteral fluids, and sulfonamides; the last two were the most effective. Following isolation of the organism, a review of the literature revealed that it produced small amounts of hydrocyanic acids. It was conceivable that the symptoms could be attributed to slow poisoning from this source. Proceeding upon this assumption, methylene blue, which had often been used effectively in this type of poisoning, was suggested as a treatment. Dr. Steffen used it and reported miraculous results with clearing of cyanosis and signs of toxicity in less than ten minutes. This affords a therapeutic test which supports the rest of the work.

MEASURES TAKEN TO STOP THE EPIDEMIC

1. The hospital autoclaved all milk until a safe milk supply could be obtained.

2. Whenever possible, stool cultures were made on mothers two weeks before they entered the hospital. Upon entry, another stool culture was made and the mothers were questioned concerning a history of diarrhea.

3. Whenever a positive stool culture was obtained, or the mother had a history of diarrhea within the past two weeks, or developed diarrhea on the obstetric floor, she was isolated on a separate floor and the infant was taken from the nursery and also isolated from the mother. If a history of diarrhea or a positive stool culture was obtained before entrance, the mother was delivered in her own room.

4. When an infant developed the first suspicious sign of diarrhea, the mother and infant were isolated and the physician notified so that treatment might be started on the infant.

5. Another room was set up for a nursery and all new infants placed in this room until all the infants in the original nursery had been discharged and the nursery could be thoroughly cleaned.

6. All mothers and infants were sent home on the fourth day routinely. The public health nurse was notified when the mother and infant were dismissed from the hospital so that a visit could be made to give the mother instructions on the care of the baby and techniques which should be used to prevent infection. If on the fourth day, the infant showed signs of diarrhea, he was sent to the pediatric department rather than home. If for some reason the mother or infant had to stay in the hospital more than four days, the mother and infant were placed in a private room and the infant kept out of the nursery.

7. Public health nurses were assigned to assist mothers leaving the hospital with newborn infants in putting into practice every precaution to safe-

guard infants from infection. Services rendered while in the home were: formula preparation; bathing; care and feeding of the infant; care of the mother while in bed; and general instructions to members of the family regarding prevention of disease. Public health nurses continued helping mothers in caring for all newborn infants until the epidemic had nearly subsided.

8. Stool cultures were repeated on all nurses in the nursery and pending report, all nurses who had had diarrhea in the past month were removed from the nursery.

The epidemic subsided within three weeks after these measures had been put into effect.

SUMMARY

1. This is a report of an epidemic of diarrhea in twenty-four newborn infants in which there were nine deaths. Eighteen of these infants probably contracted the disease in the newborn nursery. One who was discharged returned to the hospital as a feeding problem and developed diarrhea seven days later. Five developed diarrhea at home after being in contact with a case in the family.

2. The infecting organism was *Ps. aeruginosa* which gained entrance to the milk supply through a rag which was dripping into the pasteurized milk of one dairy. Bottles of dairies were exchanged without proper cleaning and sterilization, so that the organisms easily gained access to the other dairies.

3. The contaminated milk caused an epidemic of gastroenteritis in Great Bend, Kan., and caused outbreaks among patients and employees of the hospital and in consumers of the Great Bend milk in outlying towns.

4. The infants were secondarily infected by mothers and nurses who drank the milk in the hospital or by other members of the family after the infants had been dismissed from the hospital.

5. Apparently well persons who had ingested the contaminated milk acted as temporary carriers, capable of passing on the organism until they had eliminated it from the alimentary canal.

6. Of twenty-four infants studied clinically, it was possible to study nine bacteriologically. *Ps. aeruginosa* was isolated in the stools of all of the nine. Autopsy material was obtained from two cases for bacteriologic study and *Ps. aeruginosa* was isolated from both.

7. Epidemiological, milk sanitation, and bacteriologic studies, all support this conclusion, which is further supported by the therapeutic results of methylene blue.

8. The epidemic subsided within three weeks after control measures based upon the findings were put into effect.

THE EFFECT OF SALICYLATE ADMINISTRATION ON THE PROTHROMBIN TIME

CLIFTON D. GOVAN, JR., M.D.

THE prothrombin deficieney which occurs following the administration of salicylates was first demonstrated in rats by Link and his associates.[1] They suggested their findings be explained on the basis that both the salicylate compounds and the anticoagulant dicumarol liberate salicylic acid in the body which lowers the prothrombin content. Although Hanzlik[2] by in vitro experiments was unable to demonstrate the liberation of salicylic acid from salicylate compounds, later studies[3-5] confirmed Link's observations on the prothrombin changes by demonstrating a hypoprothrombinemia in man following the administration of salicylates. Among these studies, those of Fashena and Walker[5] showed the salicylate compounds tended to produce their maximum effect upon the prothrombin activity on the second day of ingestion and thereafter less and less effect was apparent despite continued therapy. Although in no instance was a normal pretreatment level of prothrombin activity reached in none of the studies were the prothrombin changes followed by periods longer than eleven days. For these reasons, a study of the prothrombin activity in patients receiving therapeutic doses of salicylates for long periods was undertaken.

In this study, an attempt was also made to correlate the changes in the prothrombin activity with the serum levels of salicylate and to determine whether the administration of salicylate compounds produced changes in the alkali reserve, blood and urine pH, respiratory rate, and urine.

METHODS

Subjects.—Twenty-four patients were included in this study. The patients ranged in age from 4 months to 11 years. Eleven were infants and thirteen were children. The ages and condition of the patients at the time the studies were begun are seen in Chart 1. No patient had received any form of salicylate medication for three weeks prior to the observation, and no other form of medication for one week prior to the study. All the subjects (except Cases 12 and 21) had received the general ward diet for at least two weeks before the beginning of the investigation.

Procedure.—On each patient, control determinations of the prothrombin time, carbon dioxide combining power, and blood and urine pH were obtained, preceding the oral administration of the salicylate. The patients were divided into groups of three. Nine infants and nine children received acetylsalicylic acid and two infants and four children received sodium salicylate. The patients in Groups 1, 2, and 3 were infants and those in Groups 4, 5, 6, and 8 were children.

From the Department of Pediatrics of Johns Hopkins University School of Medicine and the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.

Group 7 consisted of two infants and one child. Chart 2 shows the initial oral dose and form of salicylate compound received by each group. All patients who received initially less than 2 grains per pound of body weight per day were given, at four-day intervals, 0.5 grain per pound per day increase in medication until their limit of tolerance was reached. To six patients (Cases 10, 11, 12, 13, 14, and 15) on the seventeenth day of salicylate medication varying amounts of sodium bicarbonate were given simultaneously with the salicylate.

Following the initial dose of salicylate, determinations of the prothrombin time, carbon dioxide combining power, blood and urine pH, and plasma salicylate levels were performed every second, third, or fourth day during the time salicylates were being administered. These determinations were repeated the second and fourth day following cessation of medication. Urine was examined daily for pH, presence or reducing substance and albumin.

CASE	AGE	CONDITION AT ONSET OF STUDY
1	20 months	Well
2	7 months	Well
3	24 months	Well
4	11 months	Well
5	24 months	Well
6	4 months	Well
7	18 months	Well
8	19 months	Well
9	18 months	Well
10	9 years	Well
11	11 years	Acute rheumatic fever
12	3 years	Acute rheumatic fever
13	6 years	Acute hemorrhagic nephritis
14	9 years	Acute hemorrhagic nephritis
15	6 years	Acute hemorrhagic nephritis
16	6 years	Well
17	5 years	Well
18	4 years	Well
19	18 months	Well
20	19 months	Well
21	11 years	Acute rheumatic fever
22	11 years	Well
23	11 years	Well
24	10 years	Well

Chart 1.

In order to determine the effect on the prothrombin time, three patients (Cases 16, 17, and 18) were given 2 mg. of hykinone daily during the whole period of observation.

Prothrombin Test.—The prothrombin time was determined by Smith's bedside test,[6] a modification of Quick's method.[7] Desiccated rabbit's brain thromboplastin which had been stored in vacuo was used. Each determination was made using glass tubes especially cleaned and dried. A normal prothrombin time was performed with each determination. The normal controls consisted of four healthy adult interns who alternated as controls during the period of observation. For a further check of the normal variations in the prothrombin time a determination of the prothrombin time was made every three days for one

month on a mentally retarded but otherwise normal patient. A control prothrombin time was performed with each determination as described.

The prothrombin activity as determined using the following formula:

$$\text{Prothrombin activity or Clotting activity} = \frac{\text{clotting time of normal control}}{\text{clotting time of patient}} \times 100$$

For example, a patient's blood clotted in 40 seconds, a control's in 20. The prothrombin activity, therefore, was 50 per cent of normal. According to Smith and his associates[6] a clotting activity between 40 and 70 per cent is definitely in the danger zone.

The carbon dioxide combining power was determined by the Van Slyke manometric technique.[8]

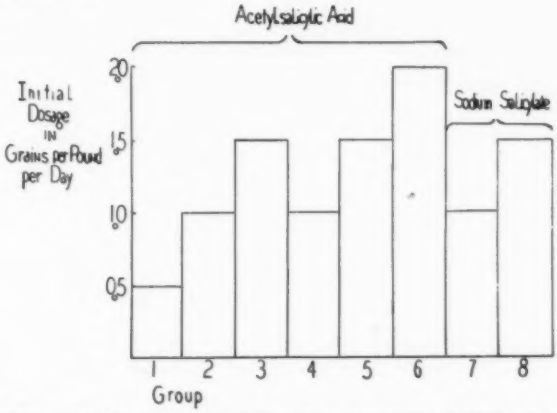

Chart 2.—Initial oral dose and form of salicylate compound received by each group.

The blood pH was determined by a colorimetric method, using phosphate buffers. The method was standardized with hydrogen electrode pH determinations. The urine pH was determined by the use of nitrazine paper.

Reducing substance found in the urine of patients receiving salicylates was roughly estimated by the standard Benedict qualitative test.

The plasma salicylate levels were determined by the method of Brodie, Udenfriend, and Coburn,[9] using 1 to 2 c.c. of serum for each determination.

OBSERVATIONS

(Charts 3 and 4)

Prothrombin Activity.—The prothrombin activity of the mentally retarded but otherwise normal patient showed a marked variation from day to day but at no time fell below 80 per cent of normal. During the period of observation, six, or approximately 25 per cent, of the patients showed an abnormal prolongation of the prothrombin time, i.e., reduction of the prothrombin activity. The most marked hypoprothrombinemia occurred between the second and fifth day

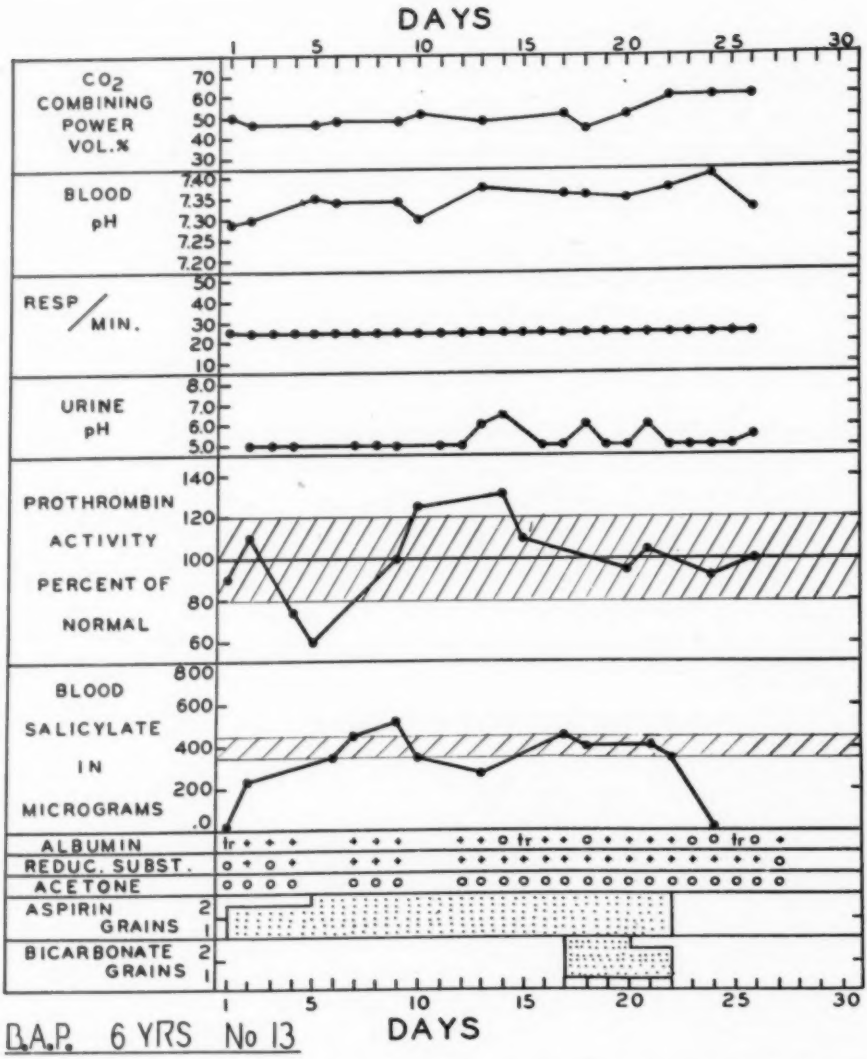

Chart 3.—This chart represents one of the six patients showing an abnormal prolongation of the prothrombin activity.

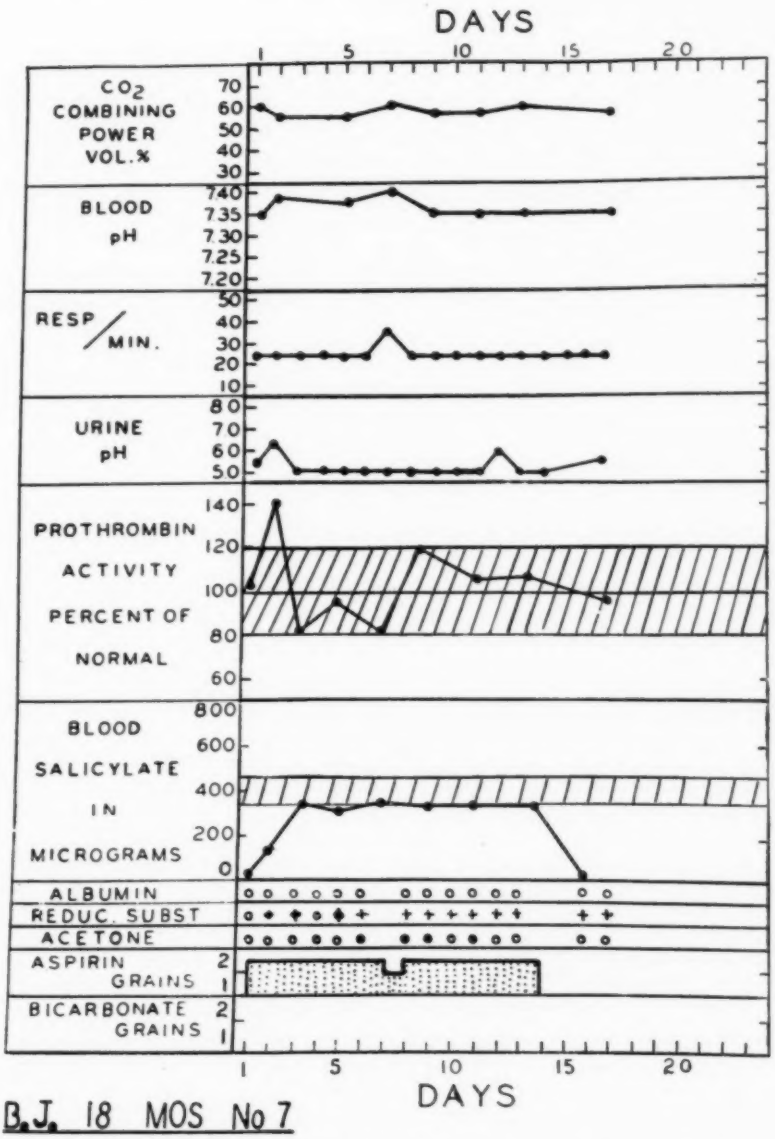

Chart 4.—This chart represents one of the eighteen patients showing no abnormal prolongation of the prothrombin activity.

of medication. In each of the six patients normal pretreatment levels of prothrombin activity were reached by the ninth day of continuous salicylate administration.

No correlation was observed between the blood salicylate levels and prothrombin time. Reduction of prothrombin activity was observed even with blood salicylate levels as low as 100 microgammas.

No difference in the effect on the clotting mechanism was observed between cases in which a sudden elevation of blood salicylate level occurred and those patients in which a gradual rise in blood salicylate level was produced.

Salicylates apparently affected, in a similar manner, the prothrombin activity in both infants and children.

It is of interest and in accord with the recent findings of Shapiro[10] and Meyer and Howard[8] that no changes in the prothrombin activity occurred in those patients receiving vitamin K.

Blood Salicylate Level.—The blood salicylate levels as determined in infants depended on the manner in which the drug was offered. High levels in the blood were more easily attained in infants when sodium salicylate in solution was given. To attain so-called therapeutic levels of blood salicylate in infants and children, doses between 1.5 and 2 grains per pound per day were required.

In most instances, blood salicylate levels were not measurable forty-eight hours after withholding salicylate medication.

Sodium bicarbonate when given in equal dosage with salicylates tended to lower the blood salicylate levels, but the striking depression as noted by Smull and her co-workers[11] was not observed.

Urinary Findings.—The urine pH revealed a tendency to shift toward the acid side, but no constancy was noted. In most instances a reducing substance was present in the urine by the second day of salicylate ingestion. On several occasions reduction of cupric sulfate to red cuprous oxide was observed. The reducing substance is thought to be a glucuronide.[5] Examination of the urine for acetone, using the Rothera test, revealed no acetone in any specimen. The presence of albumin was frequently noted, being a more common finding in the nephritic subjects.

Salicylate Intoxication.—During this study six patients developed signs of intoxication resulting from the administration of salicylates. Four were infants and two were children. Five of the six patients who developed toxic signs on salicylate therapy without bicarbonate had a slight elevation of the blood pH. In one patient no change in the pH was apparent. The signs of intoxication were not allowed to progress longer than eight hours. The signs in the order of their appearance were: (1) hyperpnea, (2) apathy, (3) anorexia, (4) vomiting, (5) fever. The patient in whom the signs appeared the most severe had blood salicylate levels far below the so-called therapeutic level. Other symptoms included vague abdominal pains and muscle pains.

DISCUSSION

The prothrombin deficiency attending the therapeutic administration of salicylate compounds is apparently neither a constant nor a dangerous feature

of this form of medication. When salicylate compounds produce a depression of the prothrombin activity, it is usually between the second and fifth day of administration of the drug and by the ninth day has usually returned to normal.

The mechanism by which salicylate compounds produce a hypoprothrombinemia is obscure. It is unlikely that the hypoprothrombinemia results from a direct action of the salicylates on the circulating prothrombin, for if such were the case the effect would be constant and dependent on the concentration of salicylates in the extracellular fluids. The observations in this study did not favor this view. It seems more likely that the depression of the prothrombin formation is a result of changes in the liver. It is well known that salicylates in very high concentrations can produce histologic changes in the livers of experimental animals. It would be anticipated therefore that similar lesions would occur in man and the degree of damage would be dependent on the concentration of salicylate in the body. Thus, if it can be assumed that the depression of prothrombin activity represents a form of liver damage, the effect of therapeutic concentrations of salicylates in the body upon the liver must be minimal. This is evidenced by the following: (1) Prothrombin deficiency does not always follow the administration of salicylates; (2) when the prothrombin activity is depressed it spontaneously returns to normal; and (3) hykinone or vitamin K will prevent a reduction of the prothrombin content.

There have been several reports of hemorrhagic complications arising during the administration of salicylates, and it is likely that hypoprothrombinemia constitutes one of the mechanisms by which this effect is produced. As has been pointed out, however, if the prothrombin activity is dependent on the amount of liver damage produced by the salicylates, it would be correct to assume that in individuals accidentally poisoned with salicylates the high concentrations would be more likely to produce hypoprothrombinemia and hemorrhages. It is in this type of patient that intensive vitamin K therapy would be indicated. However, as Link and associates[1] have pointed out, prothrombin deficiency alone does not explain the hemorrhages. It is likely, however, that vascular trauma and dilatation plus prothrombin deficiency play a part in some patients in the production of hemorrhages.

SUMMARY

1. Varying doses of salicylate were administered to twenty-four patients (eleven infants and thirteen children) over periods of fifteen to thirty-five days.

2. Eighteen patients received acetylsalicylic acid and six patients received sodium salicylate.

3. Determinations of the prothrombin time, carbon dioxide combining power, blood and urine pH, and plasma salicylate levels were made every second, third, or fourth day during the period of observation.

4. Six patients showed an abnormal prolongation of their prothrombin time or reduction of their prothrombin activity.

5. The most marked reduction of the prothrombin activity occurred between the second and fifth day of salicylate administration. In every patient, despite

continuous salicylate therapy, the prothrombin activity returned to normal by the ninth day of medication.

6. Six patients showed early signs of salicylate intoxication, during which time a slight elevation of the blood pH occurred in five. Intoxication occurred in one patient with salicylate levels as low as 100 microgammas.

7. No correlation was observed between the changes in the alkali reserve and serum levels of salicylate.

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ACID-ENZYME CONVERTED CORN SYRUP IN INFANT FEEDING

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THE purpose of this paper is to report practical experiences with an acid-enzyme corn syrup in infant feeding.*

In acid-enzyme conversion, as the name implies, cornstarch is first hydrolyzed with acid and steam until the hydrolysis has progressed to approximately the same degree as that achieved in the usual acid conversion process. It is then exposed to an enzyme which splits the residual dextrines further into maltose and dextrose. The syrup end product of acid-enzyme conversion is rich in maltose and dextrose and low in dextrines as compared to the endproduct of the straight acid conversion.

Clinical observations have been made of 2,120 artificially fed infants (Table I). Syrup containing 10 per cent added sucrose was used. The infants came from various economic levels and were deemed representative of all phases of health, illness, and growth. Many were being reared in their own homes and reported regularly to feeding clinics or doctors' offices for supervision; many were being cared for in orphanages and nursing homes; some were sickly hospitalized infants; some were newborns, full-term and premature, being cared for in an obstetric nursery. Those in the hospital groups could be classed as special feeding problems being newborn, premature, undernourished, or sick with some serious ailment. The majority, however, were normal and healthy, and were kept on their carbohydrate-containing feedings through the changes and vicissitudes attendant upon the lives of all babies.

Of the well babies, approximately 90 per cent were given whole milk in one form or another—homogenized, plain pasteurized, boiled, unboiled, diluted, or undiluted; the rest were fed evaporated milk mixtures. The sick, newborn, and premature infants in the hospitals received a wider diversity of feedings. The feedings containing the acid-enzyme corn syrup were begun at the time of weaning, or on admission to the hospital, nursing home, or feeding clinic. For those infants above 2 months of age, 1 part of syrup was added usually to 20 parts of milk; for those under 2 months the syrup was given in stronger proportions, as 1 part to 15 of milk, or 1 to 12. The infants in the various groups were chosen on an unselected and random basis. The observations extended over a three-year period.

Ease of Digestion.—In these clinical trials the acid-enzyme corn syrup proved satisfactory as a carbohydrate supplement for infant feeding. All the

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*The acid-enzyme corn syrup used in these studies was "Sweetose," manufactured by the A. E. Staley Manufacturing Company, Decatur, Illinois.

evidence indicated that it was efficiently digested and absorbed. The infants thrived and grew normally. In none of the groups was there any unusual prevalence of diarrhea, vomiting, colic, or other symptoms of gastrointestinal irritation. The small intestines and colon did not seem to be overly distended with gas. There were no attacks of hives, asthma, eczema, bloody stools, or other major manifestations of allergy attributable to the syrup.

Another index of ready digestibility was the failure of any transient disturbances to become manifest when some other form of carbohydrate supplement in the milk feeding mixture was abruptly replaced by acid-enzyme corn syrup. Most of the infants subjected to this sudden change in diet were sick infants undergoing hospitalization for some acute and serious illness. There were several hundred such instances.

TABLE I. DISTRIBUTION OF INFANTS IN THIS STUDY

	NUMBER	AGE RANGE	AVERAGE DURATION OF EXPERIMENTAL FEEDING PERIOD (WEEKS)
Infants in orphanages	700	Birth to 12 months	20
Infants raised at home	800	2 weeks to 10 months	24
Hospitalized sick infants	200	2 weeks to 12 months	2
Full-term newborns in nursery	400	Birth to 2 weeks	2
Premature newborns in nursery	20	Birth to 8 weeks	4
Total	2,120	Birth to 12 months	16

Effect on Stools.—Acid-enzyme corn syrup was not laxative in the concentrations given. Most mothers and nurses reported that the daily number of stools diminished a little or remained unaltered when infants who had been receiving maltose-dextrin preparations or simple acid converted corn syrups were changed abruptly to acid-enzyme corn syrup. The stools were usually semiformed, soft, of inoffensive odor, and nonirritating to the skin.

With twenty infants, it was thought necessary to change to a more laxative sugar in order to obtain correction for undesired constipation. Conversely, an approximately equal number of infants who had been exhibiting loose and irritating stools with other carbohydrates were described as being "improved" when acid-enzyme corn syrup was substituted.

Prelacteal Feedings.—More than 1,000 infants in the first few days of life were given boiled water containing 5 per cent acid-enzyme corn syrup. Such sweetened water proved to be well taken and gave rise to no gastrointestinal upsets.

Convenience.—Acid-enzyme corn syrup was found to be very readily soluble. Only a few minutes were required for it to go into solution even when the water or milk to which it was being added was ice cold. This quick solubility of acid-enzyme corn syrup was helpful in the preparation of feeding mixtures from unboiled, homogenized milk. With the ingredients kept cold, and the bottles permitted to grow cool before removal from the sterilizer, all manipulations of mixing and bottling could be done at refrigerator temperature.

This avoided the stimulation of bacterial growth which accompanies even a brief period of temporary warming.

SUMMARY

Milk feeding mixtures made with acid-enzyme corn syrup were fed to more than 2,000 infants of diverse ages and states of health and illness. The syrup proved highly satisfactory as a feeding supplement. It was palatable, nonlaxative, nonallergenic, provoked no gastrointestinal distress, and appeared to be efficiently digested and absorbed.

Acknowledgment is hereby made of the cooperation of the following Philadelphia institutions in securing necessary data for this study: Sheltering Arms, Florence Crittenton Home, Salvation Army Home, Homewood School, St. Vincent's Hospital and Orphanage, Rodeph Shalom Well-Baby Clinic, University of Pennsylvania Hospital, Children's Hospital, Doctor's Hospital, and Presbyterian Hospital.

SQUINT IN CHILDREN

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THE proper disposition of the child with an imbalance of the extraocular muscles is probably the most important ophthalmological problem facing the pediatrician. He is usually the first to see children with latent or obvious squint; and his responsibility does not end with their referral to an eye man. He should possess some understanding of the muscle imbalances, so that he may aid the child in securing proper care and cooperate in the giving of that care.

It is the important duty of the pediatrician to see that these youngsters do not go into adulthood untreated. At what age then should he refer these children to an eye man? In the stone age of ophthalmology the tendency was to wait in the hope that these youngsters would outgrow their "cross eyes." It is a fact that in a few cases the eyes do become straighter with advancing age, but the number is far too small to make waiting profitable. According to White, the child should be seen within two weeks after the squint is noted. Many children can be started on treatment almost immediately. Many will tolerate glasses at 18 months of age, or even less. It is well to bear in mind the fact that the macula lutae may not attain its full development until the child is about 4 months of age. All infants may periodically appear "cross eyed" before that period, as they do not have the ability to fuse images.

ETIOLOGY

All of us, normally, tend to fuse in binocular single vision; that is, to see simultaneously with both eyes. When there is obstruction to fusion, or when fusion becomes difficult, a deviation of one eye may take place. If this process occurs before the age of 16 the eye will usually deviate in; if after, it will usually deviate out.

The most common obstructions to fusion are muscle pareses and marked differences in refraction between the two eyes. Eyes which are injured, with resultant poor vision, commonly tend to deviate. These usually turn out. All squints, then, are binocular. That is, one eye fixes and the other deviates. Many individuals alternate their deviation, having the ability to fix with either eye, but not with both simultaneously.

The parents will commonly notice that the squint has occurred after some illness. Usually, in these cases, a marked difference in refraction between the two eyes will be found. The child who heretofore has been able to reconcile these differences and maintain parallelism of the two eyes unconsciously gives up the fight to maintain parallelism (orthophoria) as the result of the illness.

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The deviation results from the unconscious attempt to throw the troublesome image (of the eye with the greater refractive error) far out of the field of consciousness.

Nervous children, or those with nervous disorders, may show a squint which is not primary and which disappears when the underlying cause is removed. Again, as in tuberculous meningitis, the squint may be the first sign of a neurological disorder.

Some illnesses and certain head injuries may be followed by a paresis of one or more of the extraocular muscles. Diphtheria and meningitis are common offenders. Recently, we saw a child with a marked sixth nerve paresis following meningococcus meningitis. After three months this cleared up almost entirely, except for a slight diplopia in the extreme right field.

CLASSIFICATION AND DEFINITION

All muscle imbalances may be classified as either paralytic or nonparalytic.

They tend to fall into one of two categories: (1) phorias, or tendencies to squint and (2) tropias, or obviously manifest deviations. The first group comprises those who squint only when tired, hungry, cranky. The second group always show their squint. In a sense both are different degrees of the same process.

Three other terms, or prefixes, must also be understood. Eso (tropia or phoria) means to cross in; the so-called "cock-eye." Exo (phoria or tropia) means to deviate out; the so-called "wall-eye." Hyper (phoria or tropia) indicates that one eye is higher than the other. This latter, or vertical anomaly, is of great importance, as we shall see later on in this paper.

Classification

A—Paralytic

B—Nonparalytic

1—Accommodative

2—Nonaccommodative

All horizontal (or lateral) muscle imbalances (the eso and exo groups) tend to fall into one of the following four groups on the basis of disturbance of function:

1. Convergence excess; overconvergence for near, manifesting itself as an eso for near vision only. The eyes are parallel in distant gaze.

2. Convergence insufficiency; inability properly to converge in near vision; the eyes show an exo for near, only.

3. Divergence excess; excess of divergence for distance and parallelism in near vision.

4. Divergence insufficiency; decreased ability to diverge for distance, so that there is an eso for distance.

As a rule, a mixture of two of these eventually results; i.e., convergence excess and divergence insufficiency, with the eyes becoming crossed in for both near and distance.

PARALYTIC SQUINT

These cases are due to a complete paralysis or partial paresis of one or more of the recti or oblique muscles. Normally, the eyes are essentially parallel in all movements except that of convergence. In the paretic eye this parallelism of movement is disturbed, with a consequent diplopia in the field of action of the paralyzed muscle. This diplopia may carry over into the other fields. It is not seen in the child who is born with paresis.

The eye muscles tend to be yoked together (paired) in the performance of specific functions. For example, the right superior rectus and the left inferior oblique are "yoke" muscles in the performance of "eyes up and right."

Fig. 1.—A left hypertropia. Note that the right eye is barely elevated in the "eyes up and right" position, whereas the left eye is half buried under the brow. This is due to a paresis of the right superior rectus muscle with a "secondary deviation" or overaction of the left inferior oblique muscle.

The following will serve to illustrate the manner in which a paralysis may disturb the normal movements of the eyes (as well as their normal positions) and thus lead to ocular difficulty. If we ask the patient to look up and right, the right superior rectus and left inferior oblique act together to perform this movement. Hering's law states that an equal impulse is given to each of the functioning muscles. Let us assume that it requires a fictitious charge of 10 to move each eye up the required amount, normally. Now, if the right superior rectus is paretic and an object is presented to the left eye (the fixing or dominant eye in this case) in such a manner that the eyes must look up and right, the left will move up normally and the right partially or not at all, dependent upon the amount of paresis present.

If the right eye is now made the fixing eye, and the object presented to it, the right superior rectus will make every effort at its command to move up; and thus may exert a stimulus of say 100. This same 100 (or in this case, 10 times the required amount) will also be given to the left inferior oblique, which will now carry the left eye far up and right (Fig. 1) so that it may even be buried behind the nose. This marked overaction is referred to as the "secondary deviation" of the normal or nonparetic eye, which occurs only when the paretic eye is the fixing eye. It is an important sign in determining the existence of paresis, as it causes a marked and obvious disturbance of parallelism.

The inferior oblique, in this case, through its constant overaction, becomes a powerful muscle. Changes then tend to take place in its antagonist (the superior oblique) which now has a much stronger muscle to work against. By the same token, the right inferior rectus having a weak superior rectus to work against, also becomes stronger. Similar changes tend to take place in the other muscles; so that what started out to be a right superior rectus palsy may end by becoming an esotropia (or exotropia). The vertical anomaly is still present, but it is masked by the lateral anomaly. It is estimated that well over one-half of the lateral squints are wholly or in part due to a pre-existing vertical muscle paresis. In these cases, any treatment directed toward the lateral muscles, alone, is doomed to failure in advance.

Fig. 2.—An esotropia. The left eye is turned in. The position of the light reflexes here serves to illustrate the Hirschberg test. Note that in the right eye the light reflex is in the pupillary zone just nasal to the center of the pupil. The corresponding image in the left eye is on the cornea over the iris border.

NONPARALYTIC SQUINT

The cases in this group are due either to some defect of accommodation or of vergence function (the convergence and divergence excesses and insufficiencies) or of both.

The accommodative group can best be explained by illustration. The normal or emmetropic eye (which has no refractive error) does not accommodate for distance, accommodates 1 diopter for 1 meter, 2 for .5 meter, etc. If a child has 5 diopters of hyperopia (farsightedness) he accommodates 5 diopters for distance vision; which means that he starts with an accommodational handicap of 5. If he is now called upon to read a book at 13 inches he must accommodate 3 diopters for that distance, plus the 5 he is already using for a total of 8. As accommodation and convergence go hand in hand, he overconverges by 5, and as a result the eyes may swing in and cross for near vision. As he goes through life he will also eventually tend to cross for distance as well.

If he is a myope (nearsighted) of say 5 diopters, he cannot see in the distance clearly without glasses. An object at 13 inches, which normally requires 3 diopters of accommodation and convergence, falls into his scope of clearest vision, without calling upon the use of his accommodation, which is relaxed. With this relaxation of accommodation, there may be an associated relaxation of convergence; as a result the eyes may swing out.

Where the squint is entirely on an accommodative basis the proper refractive correction will correct the strabismus. If the squint is partially on this basis the correction will clear up that part of it.

The nonaccommodative group is on the basis of some dysfunction of either convergence or divergence, with no associated paresis. This group has already been referred to in the classification.

The term, amblyopia ex anopsia, applies to the nonaccommodative group. It refers to the cases where a marked difference in refractive errors is found, between the two eyes. For example, the right eye may require no lens and the left a +5 with a cylinder. As a result of the difference in size of the two images presented to the brain, the child may unconsciously give up using the left eye, with the result that it swings in or out. When his vision is taken, the right will be normal and the left poor. In this type of case, if seen early enough, occlusion of the right eye, plus proper correction of the left eye will correct the squint and restore useful vision to the left eye. These children may get along well until some illness intervenes; with lowered "resistance" they give up attempting to harmonize the images from eyes of dissimilar refractive errors and squint supervenes.

Fig. 3.—Exotropia of small degree. Note that the right eye is fixing, whereas the light reflex in the pupil of the left eye is more nasally situated because the left eye is deviated out, causing the image to be displaced in. In this patient the visual axis is more centrally placed than is normally the case, so that the normal right eye has its light reflex centrally placed.

DIAGNOSIS

The pediatrician is obviously not equipped to go into an extended diagnosis of most cases of strabismus. He can, however, usually determine that the child has some imbalance. Often, this is grossly visible or the mother has noted that the child squints when tired.

There are, at least, three methods by the use of which the pediatrician can rapidly note an imbalance without the necessity of making an accurate diagnosis:

1. By having the child follow some moving object (such as a toy or light) in all the fields of gaze and by noting whether the eyes are or are not parallel. A secondary deviation may be easily noted in this manner. In doing this test, it is well to examine separately up and right, straight out to the right, down

and right, and similarly on the left, rather than to swing the object rapidly in a circle, without carefully noting the position of the eyes in each separate field.

2. Hirschberg test (Figs. 2, 3). When an individual fixes on a light (as a flashlight or ophthalmoscope bulb) an image of the light will be seen in the same place in each of his pupils. Usually, this will be seen just to the nasal side of the center of the pupil, as the visual line passes nasally to the center of the pupil. If a tropia is present, the images will not be similarly located in each eye. If the left eye is turned in, the image will be seen just nasal to the center of the right pupil and far temporally to its normal position in the left eye (Fig. 2). If the left eye is turned out, the image will be far nasal to its normal position (Fig. 3). It is not uncommon to find the image (in the deviating eye) completely outside the area of the pupil, over the iris or on the sclera. This is a very good test in infants who, while uncooperative, will usually look at a light long enough for these images to be rapidly noted.

3. Screen test. If a card (the size of a calling card) is slowly passed back and forth before the eyes, as the child is fixing on a light or other object, and an appreciable movement of the eyes occurs as the card is passed from one eye to the other, it is probable that some deviation is present. This test should be done at 13 inches and for distance (20 feet or more). Whether it is of sufficient amount to require care depends upon the extent of the movement noted and upon the symptoms produced by it.

Frequently, a child with a vertical muscle imbalance will acquire a head tilt. Hence, in all head tilters, the ocular muscle imbalances should be ruled out before making a diagnosis of torticollis.

TREATMENT

There are three cardinal rules which must be observed in the institution of treatment. (1) If there are no symptoms, no treatment is necessary. This is especially true of the phorias, which can frequently occur to a considerable degree without causing any complaint. (2) Treatment must be instituted as early as possible. This will prevent the strabismus from becoming worse, as a result of muscle contractures. It may save a potentially useful eye, as in the cases of amblyopia from disuse. Early treatment saves the child from acquiring a "cock-eye" complex. It is frequently one's experience that the parents dislike having the child miss school and hence will give much more cooperation during the pre-school ages. By the same token, the child dislikes wearing an occluder while in school.

The third rule is that treatment must, as far as possible, be on a rational basis; that is, it must be predicated on a correct diagnosis. In too many quarters it is still felt that the squint surgeon's entire armamentarium consists in a recession of one lateral muscle or a resection of the other. Since, as I have already pointed out, over one-half of the cases coming to surgery have a marked deviation of one or more vertical muscles, the operative approach must be directed toward the responsible muscles. There is no place in medicine for hit or miss surgery. It must also be pointed out that the parents must understand

that one operation may be insufficient. It is better to undercorrect and to operate again, than to render a cross-eyed child wall-eyed, or vice versa.

The first step in the treatment, then, is the making of as complete a diagnosis as possible, a procedure not always possible in the infant.

The second step is a proper refraction under a cycloplegic, preferably atropine. If glasses are prescribed, they should be given a fair test of about three months; and if after that period, plus proper supplementary orthoptic exercises (if deemed necessary) the squint has not been corrected, the case should be re-evaluated with a view to surgery. It is useless for a child to wear glasses for years in the vain hope that they may eventually help. An integral part of the refraction is the occlusion of the good eye where an amblyopic eye is present. This may restore the vision of the latter so rapidly as to be almost unbelievable. It is important to be certain that the eye is actually amblyopic and not blind due to the presence of some lesion.

In the case of a recent paresis, it is advisable to wait from several months to a year, in order to give the paresis time to clear up spontaneously.

CONCLUSION

An attempt has been made to give the pediatrician some insight into the complex problem of squint, without going into too great detail on this very intricate subject.

HEART DISEASE IN CHILDREN IN A RURAL IOWA COUNTY—PARTICULARLY IN RELATION TO RHEUMATIC FEVER

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RHEUMATIC fever is one of the most serious and fatal diseases of childhood. Practically no data are available regarding the incidence of this disease in rural areas. The following report deals with a study undertaken to determine the incidence of rheumatic fever in a rural county in Iowa.

For a better understanding of the study of the incidence of rheumatic fever in Washington County, a brief review of some pertinent facts about this community is in order. The population of the county (1940 census) is 20,055. The largest town in the survey area is Washington, which has a population of 5,227. The county consists of farming and nonfarming areas. Most families live in one-family dwellings. The school population (children 5 to 19 years of age inclusive) is 5,058. The study was undertaken in cooperation with the Washington County Medical Society and the Washington County Public Health Unit. The Washington County Health Unit was set up at the request of the county medical society, and the two organizations function in close cooperation. The health unit consists of a full-time medical director, a supervising public health nurse, and two or three assisting public health nurses. The town of Washington has a full-time school nurse. The county medical society and the medical director of the health unit were extremely interested in the rheumatic fever problem and were anxious to undertake a survey in conjunction with the Iowa State Services for Crippled Children.

The school survey was carried out during the autumn of 1940. A physical examination of the heart was done for each school child by Dr. D. C. Barrett (local public health physician) under the supervision of the pediatrician, or the examination was made by the pediatrician himself. The older children were asked to find out from their parents if they had ever had rheumatic fever or chorea. The younger children were asked to have their parents fill in a questionnaire. Any child with definite or questionable heart findings or history was examined at a special clinic where complete information was obtained. The survey uncovered the following number of children with definite rheumatic fever and rheumatic heart disease, residing in the area:

11 rheumatic heart disease
3 rheumatic arthritis with questionable carditis
1 rheumatic arthritis without carditis
1 chorea without carditis

There were also six children with possible heart disease and one child with possible rheumatic fever.

We were aware that the school survey method did not reveal all children with rheumatic fever living in this area. There might well have been some in-

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stances of mild rheumatic fever which were not recognized as such at the time of the attack and which did not leave any residual damage to be recognized at the time of the school survey. It is also known from the mortality statistics of the State Department of Public Health that four school-age children of Washington County died during the years 1937 to 1940 from acute and chronic rheumatic diseases of the heart.

It was decided that more reliable and complete information on the incidence of rheumatic fever could be obtained as a by-product of several well-planned, diagnostic, and follow-up, cardiac clinics held in this area over a period of years with the cooperation of the local doctors, nurses, and school officials. Through such clinics, held at three-month intervals, we have endeavored to check every child with onset of rheumatic fever from 1940 to 1945. It is believed that this method, with community cooperation, revealed practically all of the children with rheumatic fever. The school nurse and the public health nurses checked the absenteeism of the school children and whenever a child was found to have symptoms or signs suggestive of rheumatic fever, the parents were advised to have the child seen by their physician. The family physician or the nurse reported all children with definite or suspicious findings to the public health service for further study and referral to the diagnostic clinics.

The following is a tabulation by year of onset, of the number of children experiencing an initial attack of rheumatic fever:

Year of onset	Number of school children
1940	5
1941	1
1942	4
1943	0
1944	7
1945	3
Six-year period	20

There were also six children examined who had possible rheumatic fever during this period. The average number of children per year experiencing an initial attack of rheumatic fever in this rural area of Iowa is 3.3.

The incidence of the disease in the school population for a given year for this rural county was obtained. The accumulated records of our clinics were reviewed and the incidence computed for the school population as of 1945. It was found that twenty-seven school-age children residing in this county had either rheumatic heart disease or histories of rheumatic fever without definite carditis. The mortality statistics of the State Department of Public Health (available for rheumatic fever since 1937) show four children of this school population who died from causes related to the rheumatic syndrome. Thirty-one children with rheumatic fever in a population of 5,058 give an incidence of 0.61 per cent.

All of the rheumatic subjects have been seen periodically at the cardiac clinics where diagnostic and follow-up examinations have been done. Some of the rheumatic subjects have become over age or have moved from the county. All of the subjects were living in 1945, and of the twenty-seven school-age children still residing in the county, fourteen had evidence of residual heart damage.

In reviewing the accumulated records of our clinics we also found that there were ten children of school age with congenital heart disease in this county (as of 1945). The mortality statistics of the State Department of Public Health (available for congenital heart disease since 1937) show deaths of four infants who would have been in this school population. Four additional children were found to have evidence of toxic myocarditis between 1940 and 1945.

DISCUSSION

Relative to some published incidence rates for rheumatic fever and rheumatic heart disease for areas differing in density of population and in climate, the Washington County incidence rate for school children is low. Paul[1] (1941), making a study of the incidence of rheumatic heart disease in the state of Connecticut, sampled the school population by examining all seventh-grade pupils in several industrial cities, semi-industrial cities, and rural towns. He reports the incidence of rheumatic heart disease for the industrial and semi-industrial cities and the rural towns as 4.1, 2.4, and 1.3 per cent, respectively. Sampson and associates[2] reported the incidence of rheumatic fever in school children living in Redland, California (selected because of its warm dry climate) as 0.57 per cent. The average incidence for the three California communities in this survey was 1.9 per cent. The incidence of 0.61 per cent for rheumatic fever in Washington County should be taken as a conservative estimate of the prevalence of the disease. Only subjects who had definite rheumatic fever or definite rheumatic heart disease were counted as belonging to the rheumatic group. We believe that since 1940 practically every child with rheumatic fever has been uncovered, but prior to this time a few of the school population could have had either rheumatic fever not recognized at the time or a questionable history which did not meet our criteria for inclusion in the rheumatic fever group.

Cahan[3] (1937) found the incidence of organic heart disease in the school population of Philadelphia to be 0.6 per cent. Rauh[4] (1936 to 1938) reports the incidence of organic heart disease in the Cincinnati school population to be 0.53 per cent. Of those with organic heart disease, 55 per cent had acquired lesions and 45 per cent congenital lesions. As of 1945 in Washington County there were fourteen school children with residual rheumatic heart disease and ten with congenital heart disease. For this county the incidence of organic heart disease for school children is 0.47 per cent. Of those with organic heart disease, 58 per cent have rheumatic heart disease and 42 per cent have congenital heart disease.

SUMMARY

The incidence of rheumatic fever in the school population of a rural county in Iowa is 0.61 per cent. The average number of children experiencing their first attack of rheumatic fever during each of the six years from 1940 through 1945 is 3.3. The number varied for each year from none to seven children. The incidence of organic heart disease for school children in this rural population

is 0.47 per cent. Of those with organic heart disease, 58 per cent have rheumatic heart disease and 42 per cent have congenital heart disease.

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Special Article

THE PEDIATRIC INTERN

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DURING the years of pediatric residency, the young physician formulates his approach to patients and their families. This paper discusses some of the problems confronting the intern in the hope that colleagues may find it helpful in orienting themselves.

More and more the pediatrician is called upon to focus his attention upon the parents as well as upon the child. This change in emphasis is making the pediatrician more aware of his role in the lives of parents and children. The pediatrician may well consider it a challenge to help all these people experience maximum mutual enjoyment.

THE NURSERY

The role of the pediatric intern on the newborn service is one which is only gradually attaining its deserved importance. One pediatric center has established the practice of having a full-time pediatric nursery intern who, in addition to his duties in the nursery, makes one or more home visits following the discharge of patients from the hospital.[1] In this way he is able to be of service to both mother and child in the postnatal period when trips to the pediatric clinic, superimposed on the mother's added responsibilities as well as on her physiologic weaknesses, would constitute a severe strain. Fully as important, however, is the fact that the intern, who otherwise sees patients almost exclusively in a hospital environment, gains the experience of observing the mother and infant in the home situation.

Firsthand knowledge of the home setting is a distinct asset, for without it the pediatric intern often experiences difficulty in recognizing all factors which influence the mother's attitudes during the neonatal period. He cannot be expected to know the mother's detailed life history. However, he must recognize that inadequate fulfillment of the parent's own emotional needs, sometimes going back to episodes in her own childhood, plays a role in the formation of attitudes at this trying moment. Only when aware of this can the intern adequately approach the clinical problems of the neonatal period.

Remarkable therapeutic value accrues from the investment of a few minutes daily at the mother's bedside during the post-partum period, when mother and baby are lying side by side. The mother notices the size of the baby, color of the skin, frequency or pitch of the cry, and color of the stools. Many questions arise. At this moment minor items loom large in the mother's mind. The common

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[Dr. Wessel wrote the manuscript while serving as an intern at the hospital.—Editor.]

procedure of relegating such discussions to the nurse does not mean that the intern should be unaware of them. This visit with mother and infant together, besides aiding the mother with her questions, also gives insight into the initial attitude of parent toward infant.

The intern must be aware of the many varieties of stimulus affecting the parent's attitudes. He is in a unique position to observe her initial feelings toward the new baby. An understanding intern may foresee, and possibly forestall, a feeding problem at 18 months.

One cannot overestimate the weight which mothers will place upon every remark the pediatric intern makes at this time. In many cases such casual remarks as "What a skinny baby," or "Such a big stomach," or "Such a big head," may be interpreted by the mother as indication of pathologic conditions, while in reality nothing was further from the intern's mind.

Similarly, the over-exuberant advocate of breast feeding, who outlines persuasively many of the well-known reasons for breast feeding, may be so convincing in his argument that, should there be an insufficiency of milk or some other contraindication to nursing, the mother may be certain that her infant will develop into a "weakling," may "lack immunity," or may turn out to be an "insecure infant."

Whatever positive factors there may be in favor of breast feeding, it should be clearly emphasized that a mother's unwillingness to nurse her infant must be given careful consideration before the intern uses persuasive urging. One must try to understand the factors responsible for this attitude. In many cases it is well to give up the attempt, rather than to have an unwilling mother nurse her baby "just because the doctor insisted." The majority of such situations lead to bottle feeding within a few weeks anyway, and quite frequently the early nursing experience is unsatisfactory to both mother and infant.

Thinking in pediatric circles concerning feeding habits is being considerably revised. The carefully detailed studies of Gesell and Ilg,[2] the clinical approach of Dr. Grover F. Powers and his staff in New Haven, and the popular writings of Dr. and Mrs. Aldrich[3, 4] have done much to create a more flexible attitude upon the part of pediatricians. These workers conclude that our former rigid attitudes may have been a little hasty; that babies themselves are capable of selecting a reasonable caloric intake if allowed relative self-determination. Many now consider the following to reflect a sound attitude: "Many children get along all right without clocks or scales. If your baby awakes five or ten minutes early, go ahead and feed him, and if he sleeps over time he can wait twenty or thirty minutes. You rest in the meantime. And don't worry too much over a few teaspoonfuls more or less. Most babies are pretty good judges of how much food they need."

This point deserves considerable stress. Regardless of what one considers the ideal, whether it be rigidity or flexibility of the feeding schedule, one must realize that the mother, regardless of anyone's advice, may be flexible in her own approach. A mother recently said, "Doctor, I haven't stuck to the schedule, and my baby's getting along all right. He's gaining weight, he seems happy,

and doesn't cry. But I expected you to scold me." Such an attitude on the part of the mother may well lead to a break in rapport between parent and intern, and proportionally limit his influence.

What to tell the parents of babies who appear to be somewhat retarded at birth is difficult. As is well known, there are many babies who are sluggish at birth and who continue to be sluggish for several months. The vast majority of these infants develop into normal children. Some are in the class of Mongolian idiots, others have spastic paralysis or cerebral palsy or a like condition. One's approach to the parents may be somewhat in this manner: "How does your baby look to you?" And quite frequently the mother says, "He seems a little sleepy." If this response is not forthcoming, it is wise for the intern to mention the fact in a gentle manner, and then proceed: "Your baby had a pretty tough time of it." (Or if it were an easy delivery, "Your baby does seem a bit sleepy.") Then he adds, "I think that we had better keep a pretty close watch over him for the next few months. We see many babies who seem sleepy at birth, and the vast majority develop perfectly all right. I think that your baby will be all right, but occasionally we find one baby who doesn't do so well. Therefore we want to keep an eye on your baby, and then we'll both feel better."

By the time the infant is 6 months of age, the well-trained pediatric intern can usually be more secure in his opinion. He can evaluate the developmental status, especially with the aid of Gesell standards. He can decide whether there is need of further psychometric examination. If handled properly, further examinations can give the mother the feeling that everything is being done for her infant. This may aid, rather than hinder, the mother's acceptance of the final decision. When a final conclusion has been reached, the clinical impression should be conveyed to the parents with gentle frankness and with care to give only such encouragement as is warranted.

Parents of retarded infants or of infants with congenital anomalies often have a sense of guilt. This may be latent, but occasionally it is freely expressed. The mother may feel that the infant's abnormality is related to something which occurred in her past life, either before or during pregnancy. A mother recently observed was certain that her infant had a serious congenital anomaly of the esophagus because she had gone to a night club during pregnancy.

FOLLOW-UP CLINIC

The six-week follow-up clinic gives the intern the opportunity to observe the mother, as well as the baby. Quite frequently it is the last hospital contact with the mother and infant, unless serious illness intervenes, and the remainder of well-baby activities are carried on by city health stations, or visiting nurse clinics. This is most unfortunate, since the intern loses sight of the developmental sequence of normal babies.

It is advantageous for the same intern who took care of the infant in the nursery and who saw the mother upon discharge from the hospital to see them again at the six-week period. Not only does this give the mother a sense of continuity, but also the intern can evaluate the adequacy of his earlier advice. Only in this manner can he improve his presentation and learn which points

need more emphasis. The questions which the mother poses may seem trivial to the intern, but they are important to her, and it is desirable that she have reassurance at this time.

THE OUTPATIENT CLINIC

The Parent.—The problems facing the intern in the clinic are multiple. A child is admitted to the ward with a definite disease, or at least with complaints sufficient to warrant further investigation. However, the child is brought to the clinic because the parents think that he is not well. It is the function of the clinic, not only to evaluate the health status of the child, but also to understand the curious assortment of stimuli which prompt the visit. Such factors as illness of a sibling or of a neighbor's child, periodic school health examinations, poor eating habits, and many other daily events are frequent motivations for a clinic visit, although ostensibly the stimulus is "underweight" or "poor growth." Adequate care of the child involves more than a clinical examination. The parent's motivation for the visit must be understood and discussed to his or her satisfaction.

Children referred from school because of "heart murmurs" form a group that merits serious attention. Frequently the parents have been alarmed by the note from the school, when it was intended only that the child should have a careful examination to substantiate the opinion that the murmur was functional. For those cases that are clearly functional, a few comments along this line are sufficient: "Many children have murmurs when they are born, and some keep on having them throughout life. These murmurs do not mean heart disease and there is no reason why your child cannot do everything that any child does." On the other hand, if the murmur is a suspicious one, and further study is indicated, one might say, "It does sound a little suspicious, and I think to be on the safe side we ought to have an electrocardiogram and some other tests done. Then we'll know for certain."

The question of tonsillectomy keeps recurring in a pediatric clinic. Children are frequently sent in, either by an outside physician or by school authorities, with a recommendation for tonsillectomy. In many clinics the prevailing attitude is conservative and not in concurrence with the outside recommendation. Many say, "There is no need of those tonsils coming out," and with that the interview is ended. One can go a little farther in the discussion and say, "There is considerable disagreement among physicians as to when tonsils should, and should not, come out. We are primarily interested in children here; this is a children's clinic and we do not think it wise to make a child go through an operation unless it is absolutely necessary, and unless we can be certain of improvement in the child's health. After watching children over a period of years, we have concluded that unless the tonsils are actually diseased, and not merely large, the children are better off with them in until they are somewhat older. Then if they still bother, an operation may be necessary."

Many children are brought to a clinic with the complaint that "Johnny won't eat," or "He's always fidgeting." In the majority of these cases the intern can be certain that all is organically normal. But the job has just begun.

The problem must be worked through with the parent. Basic insecurity in the mother may make her expect too much of the child and create the feeding problem which is the main complaint. The intern must realize that there is no such thing as a mother per se, or a child per se. There is a complex family situation with social, economic, emotional, and cultural factors creating the background in which the child grows up. All of these factors affect the mother and child. The intern single-handed cannot be expected to solve the emotional problems of the mother, nor even get to the bottom of them, but he can recognize their importance in the life of the child. The help of a medical social worker is invaluable in assisting the intern to understand and deal with the situation. With more difficult problems the intern may seek the aid of the child psychiatrist. He may deal with the problem himself after consultation, or the psychiatrist may take over active treatment, but the intern must remember that when the psychiatrist steps into the picture, the pediatric intern does not step out. He remains the child's physician, and must fit into the over-all picture. He must also understand where the others fit in. At one pediatric center it is customary for the psychiatrist and pediatric intern to see cases alternately, and hence both are working continually with the family. In this manner, the child receives coordinated care; and the intern, with his contact with the family and with the psychiatrist, has a unique opportunity for training.

The Child.—It is axiomatic that the intern who chooses to work in a pediatric center must have an inherent liking for children. This entails respect and understanding of the child as a person. Within the last decade there has been increased discussion of the adolescent and his difficulties in asserting his own initiative amidst the cultural patterns of society, such as the restrictions of school, community, and family. The individual personality problems of the younger child, on the other hand, have been somewhat neglected in pediatric circles. This hiatus has recently been emphasized by Aldrich,[5] who feels that we begin to think of personalities too late in the child's life. Workers in the fields of child development and psychology have continued to gather pertinent information. A new concept of the fundamental needs of the child is coming to the fore, and it includes much more than calories and vitamins.[6]

The intern must be familiar with such needs as family security and opportunity for self-expression. He has to recognize their significance in the child's development, and the effect upon the child of their inadequate fulfillment. The child, no less than the adult, needs sympathetic reassurance to help him face life's situations. For example, the problems associated with "growth spurts," as characterized by the hyperactivity of the 2½-year-old child and described by Gesell and Ilg[7] as full of "thrustrations and frustrations," appear different when considered in the light of personalitiy development. It is during such a growth spurt that "good eaters" may become "feeding problems," and children who have been well "toilet trained" may slip back into "infantile habits." One who is familiar with the norms of personality development can recognize the forces at work and can interpret to the parents the relationship to the growth processes. Considerable tact and understanding are necessary, and the

intern must remain aware that both the child and the parent need constant reassurance.

The child who is old enough to express himself should be recognized as an individual when he comes to the clinic. If possible, he should be greeted by name, and if this is not possible, a common nickname, such as "Butch," is often acceptable. After this is done consistently, for a few visits, the child will sense "He's *my* doctor." The intern who succeeds in establishing this sort of relationship with the child has already won his confidence. With the older children, it is important to get them to express their own complaints. This often leads to a clearer concept of the clinical picture. It also gives the child the feeling that the doctor is interested in *him*, and not only in what his mother has to say.

Frequently the major portion of the physical examination can be carried on while conversing with the child. It is best to leave the examination of the ears and throat to the very end. Then tell the child what to expect and perform the examination quickly and deftly. It is helpful to ask the child, "May I look at your throat?" The child will frequently answer in the affirmative, and the procedure is simplified.

When the child is ill, recommendations should be conveyed to him. Even at 3 years of age a child can be told in simple terms: "Johnny, your throat looks a little red, and I know it hurts. It seems to me that if you stay in bed for a few days, and drink lots of water and milk and orange juice, you will soon feel much better." Often advice given in this manner is more completely carried out than when it is given only to the parents. When hospitalization is necessary, one may say, "Johnny, you don't feel well, do you? I think that if you stayed for a few days—maybe a week—upstairs with lots of other children, we could help you get well quicker. Your mother can come to visit you. As soon as you are better, we'll send you right home."

Rarely a child will agree to this procedure without qualms. The important point is that it has been discussed with him. It has not been decided upon by two adults, and then told as a complete surprise to the child. He has been forewarned. In many cases the child will bite his lip, try to smile, and agree. Never tell a child that he is "to stay just overnight," when that is unlikely. It is much better to emphasize the truth, "a few days or a week maybe," than to bring in a falsehood on a pseudotherapeutic basis.

Let us consider the child who has been referred from school because of a "heart murmur." It is not sufficient for the intern to satisfy himself and the parent that all is well; the patient also must be satisfied. The child, having been sent home from school with a slip requesting further examination regarding a "heart murmur," may have been placed on limited activity by the parents. This limitation, plus parental conversations regarding "Johnny's heart" and the conversations of the other children, may have culminated in an over-consciousness of the "heart condition." Once this idea becomes fixed, it may play an important role throughout the rest of the child's life. If the intern is certain that there is no cardiac disease, let him approach the child: "Johnny, there is a little murmur, a little unusual sound there; it is the kind of sound we often

hear in children's hearts. It doesn't mean that anything is wrong. You can run around and play football and go roller skating just like other children." On the other hand, if the clinical picture warrants study, the child may be told: "I don't think that there is anything wrong with your heart, but I think we ought to make some tests so as to be certain. When we get them all done, you come back and see me and we'll talk about it."

Negative tests mean that the child can be told that all is well. If the tests show evidence of active rheumatic fever, explanation to both the parent and the child is indicated. One may say, "Johnny, the tests show that there is a little infection going on, and I am afraid that you are going to have to stay in bed for a few weeks, or maybe even longer, and then you'll feel better. If you don't stay in bed and rest up now, you'll be sicker, and then we'll be sorry." A valuable addition to this regimen is to interest the child in reading and drawing. Requesting that he bring back pictures on return visits often stimulates sedentary activities.

The child with a chronic cardiac condition necessitating limited activity presents a difficult problem. Most of these children are well enough to be up and around and to attend school, although not able to participate in athletics. They readily become chronic invalids far beyond all justification. One can approach the need for limited activity by placing the responsibility directly upon the child. "Johnny, you know as well as I do that you were pretty sick a while back, and I think that you will have to be careful for awhile. Sit down and rest when you get tired; let's leave out baseball, football, and roller skating, and maybe in a few months when you get stronger you can do more." A direct conversation with the child makes it easier for the mother to maintain the necessary limitations of activity.

It helps to arrange clinic procedures so that skilled laboratory technicians or nurses do the vaccinating and other "needle work." Then the child will have no occasion to associate a painful experience with the intern. It is important to approach the child honestly. "This *is* going to hurt a little, but we are going to have to do it. You hold still and we'll be all done in just a few minutes." Never should any painful treatment be preceded by, "This isn't going to hurt at all," when it involves a painful jab with a 3-inch needle. After an explanation many children will cooperate willingly, and it is fascinating to hear a child exclaim, "You got it, didn't you?" even after the intern has had considerable trouble in carrying out the procedure. One can often obtain the cooperation of the youngster by asking at the beginning "Which arm do you prefer?" The child often chooses an arm, and then will forget all about his original fear. An uncooperative child is scarcely an indication for severe scolding and characterizing him as a "bad boy." It is better to sympathize with the child, and say, "That *was* pretty tough, wasn't it, Sonny? But it wasn't half as bad as you expected. I'm sorry that I had to hurt you, but it's all over now."

There are many other aspects of clinic activity which might be mentioned here. For example, when referring parents and children to another clinic, be honest; tell the child and mother, "I want the doctor who knows a lot about

bones (or skin) to see you." Care must be taken not to create an atmosphere of something being "terribly wrong" because the child is being sent to another clinic. It is better to convey the idea that the aim is to utilize all the available resources.

THE WARD

The Parent.—The intern on the ward, as the representative of the hospital staff, must, in addition to giving the required medical care to his patients, deal with their families. Too often his attitude is: "We'll take care of the baby; you go home and forget about the child. That's our business." The child is, of course, the parent's business, and the intern's function includes allaying parental anxieties as well as caring for the child. In many large institutions the first contact in the hospital is a somewhat hurried interview in the admitting room. This often occurs in the early hours of the morning. The admitting physician is usually harassed by lack of sleep; the mother equally harassed by her own exhaustion and anxiety. The nurse often whisks the child out of the parent's arms and the mother is told: "That's all. Visiting hours are Tuesday from 3 to 4." Such an introduction to hospitalization can only produce increasing concern on the part of mother and child alike.

Every effort should be made to allow the parents, before they leave the hospital, to see their child safely in bed, if only through a window. It is helpful to give the mother an opportunity to talk with both the intern and the nurse who will be in charge of the child. She can then be told the hospital's method of conveying information regarding patients. If the "call system" is in effect, the intern may suggest: "Phone me between 2 and 3 o'clock tomorrow afternoon. I'll be glad to talk with you about your child." The anxious parent is often relieved by a statement like this: "The nurses and doctors on this floor are not chosen any old way. They work with children because they like children, and because they have had special training for this purpose."

It is disturbing to the child to have the parents say "good night," and add, "Mother is going downstairs for a cup of coffee, and will be back in ten minutes," when this is untrue. A nurse or intern within hearing distance can usually control such attempts. Most children will accept the statement: "Mother is going home to take care of the house and the rest of the family, and she will be back in a day or so to see how you are. As soon as you are well we will send you back home." Even with such a statement many children cry and fuss. However, the child knows the truth, and is thus spared the additional injury of losing confidence in his parents and in the doctor.

At this point parents should be told something about the child's illness. It is well to avoid exaggerations or belittling of the illness. Parents should be told only what can clearly be deduced from the history and physical examination. One can frankly say, "By morning, when we have laboratory reports and x-rays available, we will be able to tell you more."

Parents should have the illness explained to them in clear, simple terms. Meningitis, representative of an acute severe illness in children, may be handled

thus: "I think that your child is pretty sick. You know that yourself, that's why you brought him here. When a child gets a sore throat or a cold, the germ sometimes goes throughout his body, and once in a while settles inside his head. Then we say the child has meningitis. I am not certain whether your child has this or not; but by doing a lumbar puncture, that is, by sticking a needle in his back, and taking out a little fluid, and studying it in the laboratory, we can tell whether or not he does have meningitis. There are several kinds of meningitis; some are very serious, and some are not. By tomorrow we will be able to know which one, if any, he has and to tell you about the success of our treatment with other children with the same illness." The family will appreciate being allowed to call back after the lumbar puncture. If there is evidence of meningitis, they should be told. If the examination is negative, there is additional reason to report and thus relieve anxiety.

Many will disagree with this approach. Such detail, they will say, is unwarranted. I believe it to be sound practice to acquaint parents with any traumatic experience the child may encounter. Then they have a basis for interpreting the child's descriptions of "those awful needles" or "those horrible enemas," and will be less afraid that their child is being experimented upon. A child's condition, which warrants a lumbar puncture, is surely the parents' business, and it is the intern's responsibility to keep them informed.

In the case of the moderately ill child, such as one with pneumonia, the intern might say, "Your child has a very severe cold, and the x-ray reveals a small area of pneumonia. Since we have had the new drugs, pneumonia isn't as serious as it used to be, and we find that the children usually get well in a week or ten days. We like to keep them in the hospital until the x-ray shows that the chest is clear again."

The intern caring for a fatally ill child, as one sick with leucemia, is confronted with many problems. He must wait until he is certain of the diagnosis. Out of *sight* and *hearing* of the child, he may then approach the parents: "You know, your little boy is quite sick, in fact very sick. That's why you brought him here. I am afraid that he is going to be sick for quite a while. I think that we can make him a little more comfortable with blood transfusions and some medicine. But I'm sorry to say that's about all that we can do for him."

The parents should also be told that the child does not know of his fatal illness, that he has been told that he is quite sick, and that he will be sick for some time. Urge them to make him as happy as possible and to withhold their tears when in the child's presence.

Many parents impulsively want to take the child at once to another hospital. It is vital that the intern readily agree to aid in this transfer and to offer to make connections for them elsewhere. After the initial discussion or at a later date, he can often add a word or two which will discourage "shopping around," if the problem is hopeless. But initially it is better to accede. Otherwise the parents are likely to mistrust the physician. If there are known pediatric centers where new treatments are being studied, the intern should tell them frankly, avoiding unwarranted encouragement.

The Child.—The intern is at the same time physician to the child and mediator between the hospital staff and the parents. These two functions must be kept clearly in mind.

The initial physical examination of the child should be performed carefully and slowly, with every effort to gain confidence. Arriving at a tentative diagnosis, it is wise to tell the child, in words suited to his age, something about his clinical status. "Your throat looks sort of red to me, and I know it is pretty sore. We'll give you some medicine for it, and I want you to get lots of sleep and drink lots of water and fruit juice, and when your temperature stays down for a day, and your throat is all better, you will be able to go back home"; or "You have a bad cold in your chest, and the picture that we took shows a little shadow, or pneumonia, as we call it. As soon as the shadow disappears and you feel all right you can go home. We'll give you some pills so that you will get well faster."

Good rapport should be sought on this initial contact with the child, for his cooperativeness during the entire hospitalization and even future hospitalizations is dependent upon it.

The performance of lumbar puncture is an event which may occur during the first hours of hospitalization. This may have serious emotional consequences. The procedure should be explained to the child: "Johnny, in order to find out exactly what is the matter with you, and in order to make you get well quickly, we have to stick a tiny needle in your back. It is going to hurt a little, and if you hold still we'll be all done in just a few minutes." Sedation and local anesthetic are helpful.

Answer the child's questions regarding when he will be able to go home. It is sufficient to say "As soon as the x-ray shows that your chest is all clear," or "As soon as you are stronger and feel better." The intern should be careful not to be led into saying "tomorrow" or "Monday," unless it is a certainty. It is important to give the child an answer, and better that it be true to the situation, than an untruth coined in an effort at appeasement.

The maintenance of adequate fluid intake is important on a pediatric ward. It is a common practice to tell children, "Drink a lot of water or else you'll have to have the needles." In this manner, the parenteral fluid is held up as a punishment, a technique open to serious question. It is better to handle the situation in this manner: "Johnny, you should drink about ten glasses of water today. Let's see if you can drink that much, and then we won't have to bother with any needles. Okay?" The distinction between these two methods may seem trivial. In the first case the frequent "needles" are punishment. In the second case the intern is someone who is trying to help the child escape certain painful experiences which are sometimes inherent in hospitalization.

The alert intern is sensitive to the adequate psychological adjustment of the children on his ward. A quiet, shy child, who after several days still does not make friends with the other children, or a child who is continually belligerent and a troublemaker, may be an unhappy child floundering in an intolerable home or school situation. He may need expert psychiatric care.

The chronically, fatally ill child, such as one with leucemia or Hodgkin's disease, is a constant problem. After a few weeks in the hospital these children gain considerable insight into their own status, and often ask, "When will I get well?" or "Will I ever get well?" and an occasional child will say, "I know that I am not going to get better." The handling of these children is a difficult problem and necessitates the greatest possible sensitivity and sympathetic understanding. It is *not* sufficient to adopt the attitude: "He's going to die anyway, so there is no need to worry about him." One can say, "Johnny, you've been sick for many weeks. You know that as well as I do. I'm afraid that you are going to be sick for a while longer, perhaps quite a while. You are going to need a lot of rest and sleep, and pretty soon you'll feel better. But you may feel a little worse for the next few days, and you just try to make the best of it. If you have any pain, you let me know, and I'll give you some medicine that will make you more comfortable. When you feel sleepy, just try to sleep."

Care is needed in such situations to avoid giving the child a feeling of hopelessness and of being alone in the world. The intern must constantly guard against this and see to it that such a patient gets plenty of nursing attention in order to give him that added security of having someone near him.

The intern who manages to have a stock of fairy tales, poems of the "Christopher Robin" variety, or who can display familiarity with "Dick Tracy," will find it much easier to develop good rapport. Even more than adults, children have the need of socialization and conversation. The intern who can succeed on this score will win the confidence of children.

It is impossible for the intern to be an expert in all of the fields mentioned, but the large institution provides colleagues oriented in the various points of view. He may learn much from the psychiatrist and the social worker about the child's personality and the various forces which aid or impede its development. Such insight will be of inestimable value in his own relationships with children and their families, and will also better prepare the pediatric intern for the role which he will eventually play in his community, that is, the person who "knows all about children."

In short, the aim of the pediatric intern is to increase the general well-being of the child, and to learn as much as he can from each individual child who comes under his care. He must utilize all the available resources in his institution for the advantage of the child and also for his own educational advancement. By "the child" we mean a dynamic, individualistic personality with all the problems of adjustment—to family, school, community, sickness, and hospital—which surround a growing individual in our society.

SUMMARY

Various aspects and implications of the relationships between the pediatric intern and the children under his care, and their families, have been discussed. Emphasis has been placed on the ever-important factor of recognizing the individual, as well as the disease. It is hoped that this orientation may aid medical

school graduates entering pediatric services to foresee the dimensions of their relationships with children and parents. It may aid them in attaining their own goal, that of giving to those under their supervision and guidance the best possible care at the earliest possible date.

The author wishes to express his appreciation to Dr. Grover F. Powers and his staff in New Haven, and to Dr. Rustin McIntosh and his staff at the Babies Hospital, New York. The point of view expressed in this article is that which the writer developed during his pediatric training, first as a medical student in New Haven, and later as a house officer at the Babies Hospital, New York.

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The Academy Study of Child Health Services

STATE REPORTS AND THE STUDY OF CHILD HEALTH SERVICES

One of the fundamental objectives of the Study of Child Health Services is to stimulate state, county, and local agencies to inquire into health conditions within their own areas in order that health services for children may be improved. The Academy is even now well along the road toward the attainment of this objective. The extent to which it has already been reached is demonstrated by an increasing appreciation of the importance of the reports of the Study to be prepared at the state level. During recent months as the Study has progressed and as we look forward to constructive use of the factual data, the emphasis has shifted from the national report to state reports. This signficant development has arisen directly from the genuine interest and success of state chairmen, their executive secretaries, and study committees in organizing and conducting the Study in their own States. The Central Executive Staff has received repeated requests for detailed breakdowns of the statistical information suitable for a description of services and facilities for child health, not only for each State as a whole but also for the individual counties and communities within each State. The repeated question, "What information are we going to get out of the Study for our own use?" signifies that state chairmen and others who have been active in the Study are really concerned in seeing that their investments of time, effort, and money produce local as well as nation-wide results.

In response to these requests, the Executive Staff has agreed to return to the States an analysis of the information broken down to the level of counties and cities of 10,000 or more population. Despite the increased work involved, the Executive Staff has recognized the validity of the requests and has planned accordingly with a great expanded Central Office and statistical division. The addition of new staff members, described in the October issue of the JOURNAL, and the present search for adequate quarters are evidence of the intention to complete the Study in the shortest possible time.

As first announced in the August issue of the JOURNAL, three regional conferences were planned so that members of the Central Executive Staff might meet with state chairmen, executive secretaries and other state representatives for a free interchange of opinion; state representatives explaining what they wish to receive and the Central Staff describing the amount and type of material which can be made available. These meetings were held during September in Chicago, San Francisco, and Washington, D. C. From all points of view they were highly successful. All were well attended with representatives present at one or more of the three meetings from all but four States and the Territory of Hawaii. The officers of the Academy were represented by Dr. Durand at San Francisco, Dr. Hill at Washington, and Dr. Grulee at Chicago. Also a great deal of impetus was given to the Washington meeting by the presence of the Committee for the Study of Child Health Services.

Each of the meetings occupied two full days, opening with a general session at which the director of the Study described the purpose and plan of the meetings and introduced other members of the Executive Staff. Dr. Montgomery Blair, Jr., summarized the present status of the state programs and reviewed in general terms the progress of the Study to date. Mrs. Maryland Y. Pennell outlined the statistical procedures involved in editing, coding, and transcribing the data from the completed questionnaires to the punch cards, and the preparation of the tables from the punch cards. Dr. Charles L. Williams, Jr., discussed proposed methods of analyzing the material in relation to grouping of counties on the basis of their metropolitan character. This method of county classification has already

been described in some detail in the July issue of the JOURNAL (pages 117-120). The final discussion of the morning session was conducted by Dr. Katherine Bain who presented in broad terms the proposed outline for state reports.

The Executive Staff having outlined the work of the Central Office, the rest of the two-day meeting was devoted to obtaining from state chairmen or their representatives reports of progress, problems, and specific recommendations concerning the type of material to be returned to the States. There were so many questions in the minds of the Central Staff as to just what the States want that, in order to cover all details, the meeting was broken into sub-committees to consider one or more sections of the proposed state report with the specific questions and tables related thereto. A state chairman was appointed to lead the discussion of each of the five groups with a member of the Executive Staff serving as secretary for each group. The entire morning of the second day was given over to these group discussions with a general session in the afternoon at which the findings of the five groups were presented by the chairmen for open discussion.

The assignments given the five groups covered the following topics: *Sub-committee A* discussed that portion of the outline dealing with the summary section including the table forms showing volume of medical care for newborns, infants, and older children. The table forms considered by this group included those set up to answer such questions as: How does the volume of medical care vary with respect to the metropolitan and rural county groupings of the State; do differences exist in the volume of care rendered to white and nonwhite children; what is the general over-all picture of health supervision for children; what are the differences in medical and dental care in metropolitan and nonmetropolitan areas of the State? *Sub-committee B* considered information and table forms related to the distribution of physicians and dentists and the care rendered by specialists and general practitioners. Some of the questions to be answered by this section of the report included: Are physicians and dentists available in all areas of the State to care for children; are specialists as well as general practitioners available; how far do children have to travel to see a specialist; who actually takes care of the children; how many visits are made to children by general practitioners compared to the number made by pediatricians? *Sub-committee C* reviewed the table forms concerning an analysis of the practice of general practitioners, pediatricians, and dentists with regard to such specific items as: What is the age, sex, race, and medical training of general practitioners who care for children, in relation to the total number of physicians; to what extent do general practitioners request pediatric consultations; are hospitals which admit children readily available to the general practitioner; what hospital facilities are readily available to the pediatrician; what is the age, sex, race, and training of dentists who care for children? *Sub-committee D* considered information relating to hospital care for premature, newborn and other infants and older children. The table forms showing the analysis of this information were designed to answer such questions as: Where are the hospitals that admit children; what is the relation of their location to the centers of population where the children live; how many beds and bassinets do they have; what is the volume of care rendered to children by large and small hospitals; what are the variations in the type and volume of service in the metropolitan and nonmetropolitan areas; what is the location, volume of care, and character of service of the special hospitals such as tuberculosis, orthopedic, nervous and mental, contagious disease and other hospitals? This group also considered information on outpatient services, their location, volume of care rendered, and the availability of such services for pediatric specialties. *Sub-committee E* discussed the tables dealing with health supervision of children rendered by official and voluntary community health services. The factors to be analyzed include: volume of supervision given; type of personnel responsible; and location or extent of services in relation to metropolitan and rural areas. Separate table forms were reviewed for well-child conferences, dental services, mental hygiene services for children, services for physically handicapped children, communicable disease control, school health services, and public health nursing services.

These are only a few of the points which served as the basis of extensive discussions in these committee meetings. For the most part these discussions were limited to subject matter considered appropriate for state reports. There is a great deal of additional information available from the questionnaires which does not lend itself to a breakdown for each individual county. For example: in many counties there are too few pediatricians to provide sufficient information showing the characteristics of their private practice for that particular county, whereas in the national report the character of pediatric practice will be shown from the point of view of the age of children seen, the proportion of practice given to health supervision, the ratio of office, home and hospital visits, the frequency of consultations with general practitioners, the hours spent in public health activity, the extent of group practice and prepaid service, etc. Those data which are suitable for the national report but not for the state reports were described only in general and brief terms in order to complete the picture.

In the afternoon of the second day the committees reported their recommendations to the full meeting. Space does not permit a recording at the present time of all the recommendations and discussions. However, certain rather fundamental points were brought out which should be noted here.

A great deal of thought was given to the most satisfactory method of grouping counties in order to show health services available in densely populated areas where hospitals and medical centers are more apt to exist, in comparison with urban and remote sections of the country. As indicated above, this point has been described in an earlier issue of the JOURNAL and will not be repeated here except to state that a revised terminology is being used for the sake of clarity. Rather than classifying the counties as belonging to class I, II, III, IV, V, as was done heretofore, they will be given descriptive designations as greater metropolitan, lesser metropolitan, adjacent, semirural, and rural. Several of the state chairmen expressed the desire to receive the information tabulated not only in accordance with these county groupings but also for each individual county. Although this will involve considerably more work for the statistical staff it can be done for much of the data. A few of the state representatives suggested further modifications of the proposed method in accordance with trade areas in the different states. The final decision was that the Central Office will send to each state office a map showing classification of counties by the present method. These maps can then be used by the state chairman and others to determine the applicability of the method to each particular State. Suggestions for changes or regroupings of counties will then be submitted to the Central Office. A recommendation of considerable significance was that an attempt to break down the data for white and nonwhite patients was impractical, since so often the information was either not obtainable or not reliable. It was agreed that this differentiation could be made available for those States which can obtain reliable information and omit it for the others. It was also admitted with regret that it would probably be impossible to obtain reliable figures from item fourteen of schedule III-B which asks for the total number of patients seen by a pediatrician during the year.

The question of the confidential nature of certain portions of the information being obtained was again discussed. It was agreed that, when requested by the state chairmen, schedules of series I (Hospitals) and series II (Community Health Services) may be returned to state offices. However, special emphasis should be placed upon the confidential nature of the schedules of series III which deal with the private practice of physicians and dentists. The responsibility for maintaining the confidential nature of these schedules rests with the state offices until the schedules themselves are sent to the Central Office. The Central Office then assumes responsibility to keep them confidential, and will destroy them after the desired data have been transferred to punch cards. These punch cards will not include anything which might identify an individual, so that there will be no need of considering them confidential. Therefore duplicate punch cards may, if requested, be returned to States which desire to make further statistical analyses appropriate to local conditions.

Even after the free and detailed discussions of these two-day sessions, it was very apparent that there were still many unanswered questions and uncertainties as to just how the tabulated material prepared in the Central Office is to be translated into a description of child health services at the state level. It is expected with a reasonable degree of assurance that answers to many of these questions will be found during the process of preparing a report for North Carolina, our pilot State. This report is now being written by the Executive Staff in collaboration with Dr. Arthur H. London, Jr., State Chairman and member of the Academy Committee for the Study of Child Health Services. Thus, North Carolina, which was used first as a pilot in the collection of the desired information, then in the analysis of the data, is again being used as a pilot in the preparation of a suitable report. By the time tabulated data are ready to be returned to other states, the North Carolina report should be in the hands of all state chairmen to serve as a sample for those who wish to use it as such.

The present time schedule calls for a preliminary report of the North Carolina Study to be presented at the meeting of the Academy in November at Pittsburgh. By the first of the year this should have been completed and in final form subject to revision by the North Carolina Pediatric Society. By spring the schedules from all States should be in the Central Office, and at the same time material for some of the States should be ready to return to them. By summer the analysis of data should have been completed for a sufficient number of states, so that a first draft of the national report could be started, aiming at the original objective of completing the report of the nationwide Study with all States included by the beginning of 1948.

JOHN P. HUBBARD.

The Social Aspects of Medicine

THE PERMANENTE HEALTH PLAN

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The present Permanente Health Plan is an outgrowth of the medical care prepayment plan that was offered by the Henry Kaiser organization when it was engaged in huge construction projects in isolated areas.[1] Since no pre-existing medical and hospital facilities were available, these had to be provided to the many people employed. A similar problem was created after Pearl Harbor by the influx of warworkers to the areas where Kaiser was establishing shipbuilding plants. Sidney R. Garfield, M.D., who had been in charge of the medical care program during the construction of the Los Angeles Aqueduct in Southern California and the Grand Coulee Dam in Oregon, was asked to organize similar set-ups. As a result, the Northern Permanente Foundation was established to serve the employees of the shipyards in Vancouver (Washington); the Permanente Foundation Hospital in Oakland (California) and the Permanente Field Hospital in Richmond (California) for the workers of the Richmond Shipyards; and the Southern Permanente Hospital for the people employed at the steel mill in Fontana (California).

In the beginning only employees were taken care of on a prepayment plan. Dependents were able to secure medical care at the Permanente Foundation on a fee-for-service basis. Membership in the Health Plan was first opened to the immediate families of the employees at Northern Permanente in September, 1944, and at Permanente Oakland and Richmond in May, 1945. At present the Family Health Plan in the East Bay area is available to the public at large in groups or for individual membership. Quite a few employee organizations (as for example the United States Department of Agriculture, the University of California, the Key Route Transportation System) and labor unions have endorsed it.

The Vallejo Housing Projects situated twenty-five miles from Oakland and accommodating employees of the Mare Island Navy Yard contracted with the Permanente Foundation for medical care of the tenants. A Family Health Plan was organized and two outpatient clinics were established in 1945.

MAJOR PRINCIPLES

The operation[2, 3] of the Permanente Foundations is based on prepayment (to distribute the cost of medical care over a longer period of time and among a greater number of people), group practice, and adequate facilities. The Permanente Health Plan differs from the usual health insurance in that the patient deals directly with the medical organization rather than through the medium of an insurance company.

COST TO THE SUBSCRIBER AND COVERAGE

Health Plan members in Vancouver pay 80 cents a week for each adult member. Children, 16 years of age or over, are considered adult members. Fifty cents per week each is charged for the first, second, and third child under 16 years. Any other children under 16 years are covered without additional charge. Fees for membership are collected weekly by pay roll deduction from the employee-member. During vacation, illness, and temporary layoffs health protection may be retained if payment is continued.

All employees at the Kaiser Company Shipyard in Vancouver are eligible and are asked to sign up for the Health Plan when first enrolled in the shipyard. No physical examination is required for membership.

Subscribing members are entitled to physician's care up to one year's treatment for any nonindustrial injury or illness, its recurrences, and complications. Hospitalization and nursing care are given 111 days for any one illness and include food, medicines, x-rays, basal metabolism, electrocardiograms, use of surgeries and the laboratory. Private hospital room and private nurse are provided when ordered by the attending physician. Medical care for contagious diseases is included and the cost of hospitalization (at the County Hospital) is borne by the Northern Permanente Foundation. Pre-existing chronic illnesses are covered, provided the member has been on the plan for ninety days or more. A $10 charge is made for tonsillectomies for children under the age of 16 years. A $50 charge is made for maternity cases, that is, if the member has been on the plan for at least ninety days prior to delivery. This includes hospitalization and medical care before and after birth. Medicines and blood transfusions, medical and surgical supplies as used or prescribed by the attending physician are furnished, with the exception of vitamins, hormones, and permanent corrective appliances (including artificial limbs and eyes, and glasses). No dental care is given except for dental x-rays if prescribed by the attending physician for the treatment and diagnosis of systemic diseases. Ambulance service is available within a radius of thirty miles of the Foundation when deemed necessary by the doctor. Emergency service away from home is limited to $250. The treatment of mental diseases and tuberculosis is not covered (State laws provide for this care).

The Oakland-Richmond Family Health Plan is less expensive and less inclusive than the Health Plan available in Vancouver, Washington. The costs of the former are 60 cents a week to the subscriber, 75 cents for the spouse, 30 cents for one child, and 60 cents for two or more children. Diagnostic and professional service is given for pre-existing conditions but a fee is charged for hospitalization, operating room, and medication. Hospitalization for contagious diseases is not included. A charge is made for medicines prescribed for outpatients. Services covered by the Health Plan are rendered only at the Permanente Foundation Hospitals and Clinics and must be by Permanente physicians.

A fee of $2.00 is made for the first housecall by a doctor per illness. No charge is made for home visits by nurses.

All individual members who apply are subject to physical examination. This is not a requirement for group members.

An alternative plan has recently been offered. It is modeled after the Ross-Loos plan in Los Angeles. The subscriber pays 60 cents a week for himself and has full coverage as outlined in the Oakland plan, while the family is taken care of at reduced rates, namely $1.00 per office visit and a reduction of 25 per cent on laboratory procedures and x-rays. A maximum of $25 is charged for minor operations and a maximum of $100 for major operations. Hospitalization is provided at regular rates. This plan was suggested to make the Health Plan more salable, because many people feel that $8.45 a month for a family of four is more than they can afford.

ADMINISTRATION AND STAFF ORGANIZATION[2, 4]

The Permanente Foundations are charitable trusts governed by Boards of Trustees headed by members of the Kaiser family. Money to finance the original facilities was lent by Kaiser to the Permanente Foundations. They were set up in such a manner that there would not be any profit incurred by anyone in the Kaiser organization. Any funds that may be accumulated by the Foundations are supposed to be used for such purposes as medical research, provision for new facilities in areas in need of medical care, medical care for the poor, and teaching.

During the war the medical staff consisted of 75 doctors in the Oakland-Richmond area and 35 doctors in Vancouver. Fontana had 7 physicians on its staff. The amount of time spent at the hospital and outpatient departments by each doctor depends on the organization of each department and its case load.

Chief administrator of all Permanente Foundations is Sidney R. Garfield, M.D. Each hospital has a medical director appointed by him, assisted by a lay administrator.

Executive Committees consisting of the Medical Director, Chief of Staff, Heads of Departments, and elected staff officers were organized in Oakland and Vancouver by the doctors, in order to discuss policies relating to administrative and nonmedical aspects of the hospital, its personnel, and the medical care furnished. They serve in an advisory capacity only. The final decisions are made by the Chief Administrator.

There is an active staff association whose elected officers preside over regular meetings at which scientific papers are delivered and pathology conferences and clinical seminars are conducted. Business meetings of the staff association are held monthly.

There are additional committees in the Oakland hospital on Industrial Hygiene, Lay Education, Venereal Disease, Public Health, Research, and Pharmacy.

The Oakland and Vancouver hospitals have been approved for internship and mixed residencies by the Council of Medical Education and Hospitals of the American Medical Association and also for the Senior Cadet Nurse Program by the State Boards of Nurse Examiners. This not only helped to relieve the shortage of personnel but also proved to be a stimulus to the professional staff and of value in the maintenance of good quality medical care.

SALARIES OF PROFESSIONAL PERSONNEL

Most doctors are started on salaries of $400 to $600 a month. The heads of departments usually receive from $700 to $1,000 a month. A yearly increase of $1,200 per annum was given to some of the doctors during the war. Registered nurses receive from $180 to $200. Supervisors receive up to $225 a month.

FACILITIES

The Northern Permanente Foundation Hospital at Vancouver, Wash., is beautifully situated in a prune and pear orchard on a hill overlooking the shipyard and the Columbia River. It is a one-story building divided into three units. The inpatient departments are patterned in the form of Greek crosses at the centers of which are nurses' stations, drug, linen, service, and utility rooms. The operating rooms are arranged in a circle around a centralized work and sterilizing area; patients enter through exterior corridors, eliminating all cross traffic.

The hospital has a capacity of 335 beds (35 of which are for pediatrics) and averaged a daily census of 275 inpatients during the war. The outpatient department and first-aid station then handled about 1,000 to 1,500 patients a day (including approximately 75 pediatric patients).

Services include the following departments: surgery, orthopedics, obstetrics and gynecology, pediatrics, otolaryngology, ophthalmology, medicine including cardiology and endocrinology, allergy, dermatology and syphilology, urology, radiology, pathology, and clinical laboratory service.

The atmosphere is friendly. Waiting rooms are attractive and comfortable. The equipment is excellent.

The set-up in Oakland is of a similar quality and the hospital can accommodate 300 inpatients. At present it provides hospital facilities for all the Permanente units in Oakland, Richmond, and Vallejo.

The physical set-up at the Richmond Field Hospital was not as satisfactory and was overcrowded during the war years. It formerly accommodated 150 patients. It was rebuilt recently into a medical center providing outpatient care only.

ECONOMIC ASPECTS

During the war the program was financially successful in the Vancouver and the Oakland-Richmond area because of the large percentage (80 to 90 per cent) of sign-ups

for the Health Plan in the shipyards. The Family Health Plan which was started at a later date and required a separate registration was not quite as successful; 20 to 25 per cent of the original Health Plan members signed up their families.

It was estimated that during the war (1944) 40 per cent of the income of the Permanente Hospital in Oakland-Richmond was derived from what amounted to per capita payment, made by insurance companies, to the Permanente Foundation for the medical care of the employees of the Kaiser Shipyards for injuries incurred on the job. Only 5 to 10 per cent of the income was derived from private patients, and 50 to 60 per cent from Health Plan members. This changed considerably after V-J Day when the number of shipyard workers in Richmond decreased from 90,000 to 5 or 10,000. At present a considerable part of the income is derived from treating and hospitalizing private patients and by opening the hospital facilities to local private practitioners.

The number of patients on the Health Plan now is relatively small (20,000) but is increasing gradually from sign-up of new members drawn from the stable local population. The medical staff had to be cut 65 to 70 per cent.

The number of Health Plan members and doctors at Northern Permanente has been recently reduced very markedly. It is questionable whether the hospital will be able to continue its existence.

RESEARCH

Research has been done mainly in connection with clinical work. The medical department of the Oakland-Richmond hospitals has been doing significant research on the effect of double doses of sulfadiazine and penicillin in the treatment of pneumonia. The obstetrical department in Vancouver, has been doing research on the induction of labor with pituitrin and the use of spinal anesthesia in labor.

The results are published in the Permanente Foundation Medical Bulletin, a monthly magazine, and in various other medical journals.

A separate research department has just been founded in Oakland. It is supported by funds of the Foundation, the Office of Scientific Research and Development, and grants from certain drug houses. Plans are being formulated for special laboratory facilities and an animal house.

DOCTOR-PATIENT RELATIONSHIP

The factors that account for a good doctor-patient relationship are largely the same as in private practice. The personality of the doctor, his interest in the patient as a person, the amount of time he can spend on one patient, are of primary importance. A comfortable waiting room, friendly nurses and lay personnel, an adequate explanation if a person has to wait, a thorough examination, help to win the confidence of the patient.

It is evident from this, that one cannot make an unqualified statement about the reaction of the patients. Much depends on their individual experiences in the various departments and with the different doctors. New members are apt to be suspicious of the care offered by the Health Plan and fear that they won't get as much attention as they would get on a fee-for-service basis. Once they are acquainted with the set-up they often are impressed with the thoroughness of the care given and get a feeling of security because they are encouraged to return for further treatment whenever necessary.

Many of the complaints that came to the Health Plan Office during the war arose from an imperfect understanding of the Health Plan, its limitations and exclusions. Other complaints dealt with such matters as the waiting period, which was prolonged by checking the membership status and getting the clinical chart, referrals from one department to the other, and to being sent to the wrong department by lay personnel; the long waiting list for tonsillectomies; discourteous treatment by the receptionists; superficial care by the doctor. The majority of these complaints came from those places where the patient-burden for the doctor and the lay personnel was too great, as for example in the Richmond Field Hospital. The number of patients outgrew the facilities by far.

At the Oakland Hospital, which had the same medical staff as the Richmond Field Hospital but a much smaller census, the patients could be given a more personal treatment and they usually were quite satisfied. The inpatient care was almost invariably praised.

Some specialized departments make it their policy to have the patient come and see the same doctor at each subsequent visit to the department; this procedure is generally much preferred by patients and doctors alike.

There is a certain freedom of choice of physicians since most departments consist of a number of doctors; if a patient dislikes a particular doctor, he can request the service of another in the same department.

The Health Plan becomes especially appreciated in case hospitalization becomes necessary. There usually is no difficulty in securing bed space; the patient or family is not heavily burdened financially by the expenses that hospitalization and operation usually entail. Medical care is a known item in the budget of the patient.

People often resent the fact that doctors urge them to come to the hospital when they feel ill instead of visiting them at home; but when it is explained to them that all facilities for diagnosis are better and more readily available at the hospital they usually do not object.

ADVANTAGES AND DISADVANTAGES TO THE DOCTOR

One of the most important factors is that the doctor connected with the Permanente Foundations is able to give the patients, who are on the Health Plan, thorough and complete medical care without having to take the income of the patient into consideration. All the facilities of a fully equipped modern hospital are at his disposal. Most of the outpatient departments are under the same roof with the hospital facilities.

The doctor can promote his own development by the constant association with colleagues in his own and other fields, the teaching of interns and residents, and frequent staff conferences. Due to the abundance of patient material there is opportunity for specialization.

The physician can have fairly regular hours, take turns on night calls, and is insured of a definite though limited income, independent of the number of patients he sees.

The fact that he is working with a group makes him subject to problems that arise in any organization. He must follow certain rules and regulations, be able and desire to cooperate with other people, professional as well as lay personnel, and also with the administration. This is not always easy.

The security on the job depends not only on his professional ability but also on his relationship with colleagues, nurses, and patients; it is influenced by the growth or decline of the organization, by competition with doctors within the organization, and with outside doctors seeking employment at Permanente.

A factor of much controversy is the wish of the doctors to have more than advisory capacity in the administration. Most doctors feel that they want to have a more direct participation in decisions relating to the policies and financial operations of the organization.

There is no contract between the doctors and the Foundations so that employment can be and has been terminated whenever deemed advisable by the administration.

In view of the various advantages and disadvantages mentioned, it is evident that, whether a doctor likes to be connected with Permanente, depends largely on his personality, sense of values, and the importance he attaches to the aims of the organization.

Quite a few physicians were connected with Permanente because it was considered war work. After V-J Day many doctors left the organization to retire or to go in private practice, others were asked to leave because the Foundation could no longer afford to employ them due to the drop in the number of patients. Most of the physicians that remained desire to carry on this type of medical practice and hope that the necessary improvements will be made in the future.

SUMMARY AND CONCLUSIONS

1. The Permanente Foundations were organized during the war to provide medical care to the employees of the Kaiser shipyards and their families. The Permanente Health Plan

is based on the principles of group practice, prepayment, and adequate facilities. Recently the Plan became available to groups and individuals not connected with the Kaiser organizations.

2. Medical care at the Permanente Foundations is also available on a fee-for-service basis to people who are not members of the Health Plan. Since V-J Day the hospital facilities of the Oakland Permanente Hospital have been open to local private practitioners.

3. The cost of the Oakland-Richmond Family Health Plan is at present 60 cents to the subscriber, the same for spouse, 35 cents for one child, and 70 for two or more children. These charges proved to be more than a family of the middle-class income group can afford to pay. A less expensive plan has recently been offered whereby full coverage is given to the subscriber only, the family members are taken care of on a fee-for-service basis at reduced rates.

4. In order to make a group health prepayment plan economically feasible it is necessary to have a very large membership. The problem at present is to attract a sufficient number of subscribers from the permanent local population. The existing economic insecurity, migration, and unemployment make this difficult.

5. The majority of the patients are satisfied with the care given on the Health Plan. The public at large usually does not grasp the advantages unless they have been carefully explained.

6. The doctors employed at Permanente have the advantages of fairly regular working hours and a steady income, ready access to medical facilities, and consultations with other specialists on the staff, and an opportunity to practice medicine without a great financial barrier between the doctor and the patient. Most doctors feel that they would be more satisfied if their position would be more secure and if they would have more than advisory capacity in the administration.

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Proof sheets of the Permanente Foundation article were sent to Dr. Clifford Sweet, asking him if he or any other pediatricians in Oakland would care to comment on the Permanente plan. The following letter was received from Dr. Sweet which we are publishing with his permission.

EDITOR.

DEAR DR. VEEDER:

In answer to your letter of July twelfth, concerning the Permanente Foundation, I can see but slight objections to the article as it appears. I have discussed the situation with two or three of the other pediatricians who worked for them for a time. They tell me that the organization is essentially as it is described here. All of these people worked there during the war and seemed to resent principally the lack of personal freedom. So far as the pediatricians are concerned, they have taken well-trained people. I was present at the recent board meeting when the chief pediatrician, Dr. Hatoff, was a candidate. He passed with flying colors.

There are two points concerning the advantages and disadvantages for the doctors that I seriously question. One is the sentence, "Due to the abundance of patient material there is opportunity for specialization." So far as I can learn from talking with the people who have been there, there is no opportunity for specialization, except for what one gains from experience.

The other is that the physician "is insured of a definite though limited income, independent of the number of patients he sees." Like any other business organization, they do not keep anyone who does not abundantly earn his keep.

I think, on the whole, they are trying to do good work and at least during the war served a very useful purpose. Because of the laboratory and other facilities, they did much better work than was done by the average practitioner. In my mind, it is entirely possible that they are pointing the way to more general use of groups in the practice of medicine.

All of the members of the active staff at Parmanente are young physicians who have just passed their Boards or are awaiting eligibility. This thought was first brought to my mind when a father brought his infant to me saying he became uneasy at Permanente because there isn't a physician at Permanente who is not very young. Upon further inquiry, I find this to be so. It at once becomes apparent that medicine can be practiced at a small cost if only young physicians at a small salary are employed.

Sincerely,

CLIFFORD SWEET, M.D.

Oakland, California

Academy News and Notes

REPORT OF THE TREASURER

STATEMENT OF RECEIPTS AND DISBURSEMENTS, JULY 1, 1945, TO JUNE 30, 1946

Balance in checking account, July 1, 1945			$ 344.33
Balance in savings account, State Bank & Trust Company			3,838.72
Balance in savings account, First National Bank & Trust Co.			1,544.61
			$5,727.66
Receipts:			
Dues		$28,774.11	
Wartime Assessment		6,812.50	
Exhibits—January, 1946 Meeting	$8,230.00		
November, 1946 Meetings	4,732.50	12,962.50	
Initiation Fees		4,325.00	
Interest Earned		984.71	
Pamphlets—Child Health Record	432.31		
Immunization Procedures	434.60		
Vitamins	18.80	885.71	
Subscriptions—Men in service		917.25	
Committee—Post-War Courses		10,000.00	
Bonds sold		10,000.00	75,661.78
			$81,389.44
Disbursements:			
Annual Meeting—January, 1946		3,984.97	
November, 1946		124.00	4,108.97
Bank charge and exchange			129.23
Certificates and mounting			74.03
Executive Board			3,403.22
Miscellaneous			297.57
Office supplies and equipment			225.19
Postage			655.67
Rent			2,752.71
Salaries—Secretary		9,750.00	
Assistant Secretary		1,450.00	
Stenographer		2,640.00	
Office		1,543.71	15,383.71
Stationary and printing			1,709.48
Subscriptions			7,980.00
Telephone and telegrams			521.30
Travel—Secretary			495.57
Treasurers' Bonds			85.00
Expense—Region I		402.60	
Region II		10.00	
Region III		86.91	
Region IV		36.94	
Region V		2,054.40	2,590.85
Expense—States (Region I)		77.24	
(Region II)		30.26	
(Region III)		52.27	
(Region IV)		18.59	178.36

Expense—Committees			
Cooperation with American Legion	395.21		
Legislation	25.00		
Post-War Courses	1,507.93		
Post-War Planning	17,348.52		
Rheumatic Fever	100.00		
Special	22.05	19,398.71	
Pamphlets—Child Health Record	407.66		
Immunization Procedures	28.96		
Vitamins	.78	437.40	60,426.97
Balance—June 30, 1946			$20,962.47

Balance in checking account, June 30, 1946	$11,187.49
Balance in savings account, State Bank & Trust Company	8,214.89
Balance in savings account, First National Bank & Trust Co.	1,560.09
	$20,962.47

The following Fellows of the Academy have been released from service:

Army

Richard J. Lien, St. Paul, Minn.
Edward B. Plattner, Chicago, Ill.
Thomas E. Shaffer, Columbus, Ohio

Navy

Wesley S. Nock, Miami, Fla.
W. S. Nolting, Detroit, Mich.
Arthur H. Spreen, Cincinnati, Ohio
Morris Steiner, Brooklyn, N. Y.
William R. Wilson, New Haven, Conn.

Wesley S. Nock, Miami, Fla., has been promoted to Lieutenant Commander in the Navy.

News and Notes

CAMPAIGN TO COMBAT HEART DISEASE

The initiation of a nationwide program of public education and information on diseases of the heart was announced by officials of the American Heart Association, Inc.

The program, according to Dr. Howard F. West of Los Angeles, president of the association, will have as its prime purpose "the dissemination of educational information to the public in a broad effort to retard the rapid increase of heart disease throughout the nation."

Officials of the American Heart Association state that the association's program will call for emphasis on educational work with schools, parent-teachers' associations, and other groups concerned with children because of the importance of rheumatic fever and heart disease. According to recent surveys, this scourge of children causes more than five times as many deaths as the combined total of deaths from infantile paralysis, scarlet fever, diphtheria, measles, meningitis, and whooping cough. It is a serious disease among adults, too, as illustrated by the estimated 40,000 veterans who acquired the disease during their recent military service. The war forcibly dramatized the need for a national health program designed to retard the increase in heart disease cases. An estimated 10 per cent of the men rejected by the United States Selective Service were disqualified because of cardiovascular diseases (diseases of the heart and blood vessels).

The educational campaign of the American Heart Association will reach its climax during National Heart Week to begin on February 9, 1947, which includes St. Valentine's Day. It is expected that all branches of medicine, pharmacy, insurance, industry and many other groups interested in health and public welfare will cooperate fully.

Supporting and cooperating groups will include the following national organizations which comprise the American Council on Rheumatic Fever of the American Heart Association:

American Academy of Pediatrics
American Association of Medical Social Workers
American College of Physicians
American Hospital Association
American Medical Association
American Nurses Association
American Public Health Association
American Rheumatism Association
American School Health Association
National Organization for Public Health Nursing
National Society for Crippled Children and Adults

The collaboration of the United States Public Health Service, National Tuberculosis Association, and others is expected.

Local Heart Associations and Affiliated groups in such cities as New York, Washington, Chicago, Boston, will assist in the national campaign.